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Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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2 figures
2 tables

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Abstract

Objectives

To assess the effect of antihypertensive treatment in the 130-140 mm Hg systolic blood pressure range.

Design

Systematic review and meta-analysis.

Information sources

PubMed, CDSR and DARE were searched for systematic reviews, which were manually browsed for clinical trials. PubMed and CENTRAL were searched for trials directly.

Eligibility criteria

Randomized double-blind trials with ≥ 1000 patient-years of follow-up, comparing any antihypertensive agent against placebo..

Data extraction and risk of bias

Two reviewers extracted study-level data, and assessed risk of bias using Cochrane Collaborations risk of bias assessment tool, independently.

Main outcomes and measures

Primary outcomes were all-cause mortality, major cardiovascular events and discontinuation due to adverse events. Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related adverse events and renal impairment.

Results

Eighteen trials, including 92 567 participants (34 % women, mean age 63 years), fulfilled the inclusion criteria. Primary preventive antihypertensive treatment was associated with a neutral effect on all-cause mortality (relative risk 1.00, 95 % confidence interval 0.95 to 1.06) and major cardiovascular events (1.01, 0.96 to 1.05), but an increased risk of discontinuation due to adverse events (1.23, 1.03 to 1.47). None of the secondary efficacy outcomes were significantly reduced, but the risk of hypotension-related adverse events increased with treatment (1.71, 1.32 to 2.22). In coronary artery disease secondary prevention, antihypertensive treatment was associated with reduced risk of all-cause mortality (0.91, 0.83 to 0.99) and major cardiovascular events (0.85, 0.77 to 0.94), but doubled the risk of adverse events leading to discontinuation (2.05, 1.62 to 2.61).

Conclusion

Primary preventive blood pressure lowering in the 130 to 140 mm Hg systolic blood pressure range adds no cardiovascular benefit, but increases the risk of adverse events. In secondary prevention benefits should be weighed against harms.

Registration

Registered in PROSPERO, registration number CRD42018088642.

Article Summary

Strengths and limitations of this study

- Meta-analysis restricted to randomized double-blind placebo-controlled trials, thereby minimizing the risk of performance bias
- Adverse events included as co-primary outcome, putting emphasis on both benefits and harms
- Separate analyses for primary and secondary preventive trials, reducing the risk of confounding from coronary artery disease and increasing the usefulness of the results in different clinical contexts
- Main limitation is the use of study-level data, with the potential for ecological bias.

Introduction

For decades, hypertension has been defined as a blood pressure (BP) ≥ 140/90 mm Hg.[1] The definition has been uniform across the world, and for most patients the recommended treatment goal has been < 140/90 mm Hg.[2-4] In 2017, the American Collage of Cardiology (ACC) and the American Heart Association (AHA) updated the U.S. guidelines, changing the definition of hypertension to ≥ 130/80 mm Hg.[5] For secondary preventive patients, and for primary preventive patients with a 10-year cardiovascular risk ≥ 10 per cent, the treatment goal is now < 130/80 mm Hg. Recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) followed, retaining the old definition of hypertension, but lowering the treatment goal to 120-130/70-80 mm Hg for most patients [6]

The revision of both sets of guidelines were heavily influenced by the Systolic Blood Pressure Intervention Trial (SPRINT).[7] SPRINT randomized > 9 000 high-risk patients (without previous stroke or diabetes) to a systolic blood pressure (SBP) target < 120 mm Hg compared to < 140 mm Hg, and was stopped preterm due to lower risk of death and cardiovascular disease in the intensive treatment group.[7] In addition to SPRINT, the ACC/AHA performed a systematic review and meta-analysis including only non-blinded randomized trials comparing different treatment goals.[8]

Blinding of participants and study personnel is desirable to minimize the risk of performance bias.[9] In non-blinded studies, such as SPRINT and those included in the ACC/AHA systematic review, participants may be handled differently depending on treatment group, thereby cofounding the assessment of the intervention. Meta-epidemiological studies have found that trials with unclear or incomplete blinding

produce more favourable results compared to trials that are double-blind.[10] Additionally, in the clinic, we know the patients' blood pressure, but not what blood pressure he or she will have after adding an additional drug. Placebo-controlled trials mimic the clinical situation where the question is – should we add another drug or not?

This systematic review and meta-analysis aims to evaluate the benefits and harms associated with antihypertensive treatment in randomized double-blind placebo-controlled trials with mean SBP 130-140 mm Hg at randomization. Such an approach eliminates the risk of performance bias, yet produces treatment effect estimates reasonably specific for the SBP interval for which the new recommendations differ from previous ones.

Methods

We performed a systematic review and meta-analysis guided by the recommendations from the Cochrane Collaboration.[9] A protocol was registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42018088642. Reporting follows the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Studies were eligible if they were randomized double-blind placebo-controlled trials with ≥ 1000 patient-years of follow-up; assessing the effect of any antihypertensive agent against placebo, with mean baseline SBP ≥ 130 mm Hg and < 140 mm Hg. Target-driven trials were excluded due to reasons described above, and trials comparing different antihypertensive agents against each other were excluded because they risk

assessing blood pressure-independent effects of agents. [9,10] We also excluded trials in patients with acute myocardial infarction or heart failure/left ventricular dysfunction because several antihypertensive agents are thought to have blood pressure independent effects on clinical outcomes in these settings.[12,13]

We used one of our recent, more comprehensive systematic reviews for study selection.[14] Search strategies for the previous review are presented in the online supplement (eMethods). In addition, we searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from the date of the previous search until February 2018, using search terms ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke). Titles were screened by M.B. and apparently irrelevant publications were removed. Two authors judged abstracts separately, after which final decision on eligibility was reached through discussion (eFigure 1).

Data were extracted from the included studies into specially designed Excel sheets by two authors separately. When extracted data differed between authors, we revisited original publications. Descriptive data were collected on study level, whereas blood pressure data and outcome data were collected for each treatment group individually. All trials were judged for risk of bias by two authors separately, using Cochrane Collaboration´s Risk of Bias assessment tool.[15] The risk of bias tool covers six specific domains related to randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, attrition and outcome reporting. Also, we assessed sponsor involvement, protocol changes and premature study discontinuation as other potential sources of bias. Trials judged to be at high risk of selection bias,

performance bias, detection bias or attrition bias (first five domains), were excluded from all analyses (eTable 1). Risk of bias for selective reporting should be considered interpreting the overall analyses for each outcome rather than individual trials, because it is the lack of data rather than biased data that may produce biased overall results.

Primary outcomes were all-cause mortality, MACE (defined as cardiovascular death, myocardial infarction and stroke if not specified otherwise), and discontinuation due to adverse events (AEs). Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related AEs, and discontinuation due to renal impairment/acute kidney injury.

Results were analyzed according to the intention-to-treat principle, in the sense that participants were analyzed in their assigned treatment group. When study participants were lost to follow-up, relative risks (RR) were calculated using complete cases in the denominator, according to the recommendations from the Cochrane Collaboration.[9] In two sets of sensitivity analyses, we calculated RRs using the observed number of events in the numerator and the total number of randomized participants in the denominator (assuming that all participants lost to follow-up were event free), and the observed number of events plus number of participants lost to follow-up in the numerator and the total number of randomized participants in the denominator (assuming that all participants lost to follow-up had experienced an event). RRs were not standardized for BP differences in trials, because such standardization is associated with increased heterogeneity, unbalanced study weights, and biased overall results.[16]

Relative risks from individual trials were pooled using DerSimonian-Laird random-effects meta-analyses. We separated primary preventive studies from studies in people with established coronary artery disease (CAD), because these represent clinically different populations, and because we have previously observed potentially different treatment effects in these groups.[14] Trials with mixed populations were classified as CAD trials if ≥ 50 % of participants had previous CAD. Treatment effect interaction between primary preventive studies and CAD studies was assessed using random-effects metaregression. Pre-specified sensitivity analyses, excluding trials in people with diabetes, trials of dual renin-angiotensin-aldosterone system (RAAS) inhibition, trials not reaching < 130 mm Hg in the intervention group, trials of previously treated/hypertensive patients, and trials of treatment naïve patients, were performed to test the impact of different patient/trial characteristics on overall results for primary outcomes. We explored potential effect modification by diabetes and absolute cardiovascular risk as continuous explanatory variables using random-effects metaregression. Lastly, we performed ad-hoc subgroup analyses, stratifying primary preventive trials by 10-year MACE event-rate above versus below 10 %, to approximate the cut-off used in the 2017 ACC/AHA guidelines.[5]

Between-study heterogeneity in meta-analyses was assessed calculating I-squared, which represents the percentage of variance between studies that cannot be explained by chance alone. When statistical heterogeneity was present we sought for corresponding clinical heterogeneity. If statistically deviating studies differed with respect to clinical characteristics, they were excluded in sensitivity analyses. Small-study effects were assessed through funnel plots for all primary and secondary

outcomes, using Harbord´s test for asymmetry.[17] All analyses were performed using STATA v12.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advice on interpretation or writing up of results. Since we used only aggregated data from previous trials, we are unable to disseminate the results of the research to study participants directly.

Results

Eighteen trials[18-35], including 92 567 participants (34 % women; mean age 63 years), fulfilled the inclusion criteria (table 1). During an average of 4.5 years under randomized double-blind treatment, 2 042 participants were lost to follow-up (2.2 %), resulting in 90 525 complete cases and 407 000 patient-years of follow-up. Twelve trials[19-22,25-27,30-33,35], including 54 020 participants, were classified as primary preventive. Mean baseline SBP in these trials was 138 mm Hg, and mean SBP difference between treatment groups during follow-up was 3.4 mm Hg. Six trials[18,23,24,28,29,34], including 38 547 participants, were classified as CAD trials; mean baseline SBP was 137 mm Hg, with 4.2 mm Hg SBP difference during follow-up.

In primary prevention (figure 1), treatment was not associated with any effect on all-cause mortality (relative risk 1.00, 95 % confidence interval 0.95 to 1.06) or MACE (1.01, 0.96 to 1.05), but an increased risk of AEs leading to discontinuation (1.23, 1.03 to

1.47). In CAD trials (figure 2), treatment reduced the risk of all-cause mortality by 9 % (0.91, 0.83 to 0.99), and the risk of MACE by 15 % (0.85, 0.77 to 0.94), but doubled the risk of AEs leading to discontinuation (2.05, 1.62 to 2.61). Heterogeneity was low in mortality and MACE analyses for primary prevention, moderate to high in CAD trials, and very high for AEs in both cohorts. The difference between primary preventive trials and CAD trials was significant for MACE (p=0.019) and borderline for all-cause mortality and AEs (p=0.051 respectively 0.070).

None of the secondary efficacy outcomes were affected by primary preventive treatment (table 2; online supplement eFigure 2-7). Hypotension-related AEs increased by 71 % (1.71, 1.32 to 2.22) whereas discontinuation due to renal impairment showed a non-significant tendency towards harm (1.20, 0.93 to 1.55). Of note, heterogeneity was high in the renal impairment analysis, mostly due to one study in patients with type 1-diabetes and macroalbuminuria.[26] When this study was removed in a sensitivity analysis, heterogeneity decreased and the observed risk increase became nominally significant (1.30, 1.06 to 1.58).

In CAD trials (table 2; online supplement eFigure 2-7), treatment reduced the risk of myocardial infarction (0.83, 0.72 to 0.97), stroke (0.79, 0.66 to 0.94), heart failure (0.76, 0.67 to 0.86), and cardiovascular death (0.86, 0.74 to 1.00, p=0.047). Differences between primary prevention and CAD trials were significant or borderline significant for all efficacy outcomes except stroke (eFigure 2-7). The relative risk of adverse events was similar as in primary preventive studies, although estimates were less precise and reporting was poor (only one trial reported renal impairment).

Sensitivity analyses, testing the impact of different trial characteristics, shifted effect estimates slightly (eFigure 8-12), but not enough to affect the interpretation of our main findings. Metaregression analyses, exploring potential effect modification by observed cardiovascular risk and diabetes mellitus were non-significant. Of note, the absolute 10-years risk of MACE was well above the 10% threshold for recommending treatment in the ACC/AHA guidelines, with an average risk across studies of 26 % (eTable 2); subgroup analyses of primary preventive trials stratified by 10-year cardiovascular event-rate found no interaction between risk of MACE and treatment effect (eFigure 13).

Risk of bias was generally judged as low for individual trials (eTable 3 & eResults). We required studies to be described as randomized double-blind placebo-controlled trials to be eligible. Loss to follow-up was limited, and sensitivity analyses imputing all participants lost to follow-up as either having an event or being event-free did not alter effect estimates (eFigure 14-15). Three trials were judged to be at high risk of bias for individual domains.[20,24,26] We performed sensitivity analyses, testing the impact of these trials on our primary outcomes (eFigure 16). This had marginal effects on relative risks and confidence intervals, but no effect on nominal significance for any analysis.

Funnel plots showed no signs of asymmetry (eFigure 17-25), with the possible exception of hypotension-related adverse events (p=0.06). When we explored this further, we found that treatment effect correlated with number of events but not study size (eTable 4). The frequency of hypotension-related AEs varied by a factor of 50 between trials, presumably representing different thresholds for reporting. Thus, the observed association between number of adverse events and the relative risk of adverse

events might represent a stronger association between treatment and severe events compared to less severe events.

Discussion

This systematic review and meta-analysis evaluates if antihypertensive treatment in the 130-140 mm Hg SBP interval is supported by findings from randomized double-blind placebo-controlled trials. This does not seem to be the case in primary prevention, with no treatment effect on all-cause mortality or MACE, but an increased risk of AEs leading to discontinuation. In people with previous CAD, treatment might be beneficial, although these findings should be interpreted more cautiously due to statistical heterogeneity and wider confidence intervals. Overall, the results presented here question the recent shift in SBP treatment goals from 140 mm Hg to 130 mm Hg for the majority of patients, seen on both sides of the Atlantic.[5,6]

This paper has several important limitations that need to be addressed. Firstly, we only had access to aggregated data, making analyses susceptible to ecological bias. Studies were included based on average SBP levels, meaning that individual participants with an SBP > 140 mm Hg or < 130 mm Hg were included in the analyses because the average SBP in their trials were within the accepted range. Similarly, individual participants with an SBP within our accepted range were missed because they were included in trials with an average SBP outside our accepted range. Notably, this problem is not unique to this review, but applies to most meta-analyses in the field, including those comparing different blood pressure targets cited by guidelines. [8,36,37] Overcoming this would require individual-patient data, unfortunately not available to date. Secondly, the

aggregated nature of our data also affects categorization of trials as primary or secondary preventive. In trials categorized as primary preventive, 17 % of participants had CAD, whereas in secondary preventive trials the corresponding number was 95 %. This represents reasonable separation between groups, although this aspect could also be explored further in individual-patient data meta-analyses. Thirdly, SBP was only moderately reduced in the trials included in our analyses; less so compared to previous meta-analyses including target-driven trials. Although a less pronounced effect on clinical outcomes would be expected, the observed SBP difference of 3.4 mm Hg during > 200 000 person-years of follow-up should have resulted in at least a tendency towards primary preventive benefit if such were present. Instead confidence intervals were fairly narrow around the null effect.

The arguments for lowering SBP treatment goals differ slightly between the ACC/AHA guidelines compared to the ESH/ESC guidelines.[5,6] Common to both sets of guidelines is that they put emphasis on the results of systematic reviews and meta-analysis. Whereas the ACC/AHA performed their own systematic review of trials comparing different targets,[8] the ESH/ESC refers mainly to two previously published papers combining results from target-trials and placebo-controlled trials.[36,37]

The main strength of this review, compared to the systematic reviews underlying the ACC/AHA and the ESH/ESC guidelines, is that it is limited to randomized double-blind placebo-controlled trials, protecting it against performance bias. Although the magnitude of this potential problem is unknown, target-driven trials may be susceptible to performance bias due to their non-blinded nature.[9] Possible indicators of such bias might be 20-30 % more unscheduled visits in the intensive treatment group, and a large

non-cardiovascular component of the all-cause mortality reduction, seen in SPRINT.[7] Meta-analyses restricted to target-trials, such as the one by the ACC/AHA[8], may be especially susceptible to these kinds of biases, whereas the risk is probably lower in meta-analyses combing target-trials and placebo-controlled trials, such as those underlying the ESH/ESC recommendations.[36,37] Notwithstanding, the different findings in our analysis compared to the ACC/AHA analysis should raise the question if performance bias does play a role in target-trials of antihypertensive treatment, exaggerating treatment effect estimates.

Another important difference between this analysis and the ones underlying the ACC/AHA and ESH/ESC guidelines is that we analyze primary preventive studies and secondary preventive studies separately. This is important because the evidence for BP lowering in the 130-140 mm Hg interval comes to a large extent from trials in people with established coronary artery disease (CAD). Before primary and secondary preventive trials are combined one has to ask if it is reasonable to extrapolate findings from CAD patients to healthy individuals. To answer this, it is important to consider possible mechanistic differences in these populations. In primary prevention, development of atherosclerosis is a sine qua non for succeeding cardiovascular events, and hence the effect of BP lowering treatment on the early stages of atherosclerosis becomes most important. In people with established CAD, on the other hand, angina and heart failure symptoms are closely related to myocardial oxygen balance, depending to a large extent on cardiac afterload which is proportional to systolic blood pressure.[38] Also, systolic blood pressure has been associated with changes in atheroma size, indicating that higher blood pressure may increase the risk of plaque rupture.[39] Therefore, it is not beyond reasonable doubt that BP lowering might work through different mechanisms

depending on CAD status; in this situation, lumping trials with and without CAD patients should be avoided. The analyses presented here provide statistical support to the pathophysiologically based decision to separate patient categories. Indeed, it shows that the observed benefit in previous analyses depends on inclusion of secondary preventive studies.

Lastly, the systematic reviews referred to as supportive of lower treatment targets in the ESH/ESC guidelines used meta-analyses standardized to systolic BP reductions of 10 mm Hg.[36,37] This might seem reasonable at first, but affects the results in ways that might not be clear to most readers.[16] Firstly, standardization amplifies treatment effects by about 50 %, because SBP reduction in the included trials was on average 6-8 mm Hg whereas results are standardized to 10 mm Hg. Secondly, standardization assumes that there is a linear association between blood pressure reduction and cardiovascular outcomes, which may not be the case in this blood pressure interval and may also be different for different outcomes. If indeed the association between BP reduction and cardiovascular event reduction were linear, one would expect decreased heterogeneity with standardization. Our previous results indicate that standardization increases heterogeneity and makes analyses highly sensitive to choice of statistical methods.[16] This is probably due to amplification of differences not related to BP lowering, paradoxically making standardized results less blood pressure-dependent. Thirdly, standardization of standard errors, which was applied in one of the referred meta-analyses, disrupts the association between number of events within trials and weight given to trials in meta-analyses.[16,36] For example, the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial, were given 7.3 % weight the all-cause

mortality analysis, despite contributing with less than 0.3 % of participants.[36] Simply put, standardization makes results less representative of the underlying data.

Although arguments can be made for including target-trials, lumping different populations and using standardization, all these approaches build on assumptions that the current analysis does not. If treatment benefit hinges on these assumptions, results are simply not robust enough to change guidelines for hundreds of millions of people worldwide. Meta-analyses using non-standardized methods have consistently found that the effects of antihypertensive treatment are attenuated at lower BP levels.[14,40-42] In a recent paper, we found 22 % reduced risk of MACE if baseline SBP was > 160 mm Hg, 12 % reduced risk in the 140-159 mm Hg SBP range, whereas in trials with baseline SBP below 140 mm Hg treatment effect was neutral for all efficacy outcomes. These results are well in line with the third Heart Outcomes Prevention Evaluation (HOPE-3) study, where 12 705 participants with average baseline BP 138/82 mm Hg were randomized to candesartan/hydrochlorothiazide combination therapy or matching placebo.[25] In fact, HOPE-3 is the only mega-trial aiming to assess the effect of antihypertensive treatment against double-blind placebo in mostly treatment naïve normotensive primary preventive patients. Neither the primary combined endpoints nor individual cardiovascular outcomes were reduced by treatment. However, there was a significant interaction between baseline SBP and treatment effect on MACE, with treatment benefit in the highest SBP tertile but a tendency towards harm in the lowest SBP tertile.

Treatment decisions should always be based on consideration of both benefit and harm. In situations where interventions are unlikely to be harmful, one may consider treatment despite weak or conflicting evidence. Unfortunately, randomized clinical

trials, and systematic reviews of such trials, show incriminating signs of harm for antihypertensive treatment at BP levels now recommended in guidelines. In people with diabetes mellitus, we have previously shown that BP-lowering treatment at SBP levels < 140 mm Hg is associated with 15 % increased risk of cardiovascular death.[40] Further down the ladder of seriousness and irreversibility comes an increased risk of chronic kidney disease,[43] acute kidney injury,[44] as well as hypotension-related adverse events and adverse events leading to treatment discontinuation presented here.

In summary, randomized double-blind placebo-controlled trials do not support primary preventive BP-lowering in the 130-140 mm Hg SBP range. Such treatment does not affect all-cause mortality or incident cardiovascular disease, but increases the risk of adverse events. In people with previous CAD, treatment may reduce the risk of all-cause mortality and MACE, at the cost of more pronounced risk increase for adverse events. In CAD patients, therefore, benefits should be balanced against potential harms for individual patients.

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Data sharing: This study analyzed previously published data that are available to readers through the cited references. All data used for outcome analyses are presented in the article or its online supplement.

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Table 1. Study characteristics

Acronym (year)	Participants (n, age, sex)	Co-morbidity	Intervention/ Control	Baseline SBP/DBP (mm Hg)	SBP/DBP difference (mm Hg)
ACTION (2004)	7665 63 years 21 % female	100 % CAD 14 % DM	Nifedipine 60 mg vs. placebo	137.5/ 79.8	5.7/ 3.0
ACTIVE I (2011)	9016 70 years 29 % female	36 % CAD 20 % DM 100 % AF	Irbesartan 300 mg vs. placebo	138.3/ 82.4	2.9/ 1.9
ALTITUDE (2012)	8561 64 years 32 % female	26 % CAD 100 % DM 98 % CKD	Aliskiren 300 mg vs. placebo	137.3/ 74.2	1.3/ 0.6
BCAPS (2001)	793 62 years 55 % female	4 % CAD 3 % DM All had carotid plaques	Metoprolol CR/XL 25 mg vs. placebo	138.9/ 84.7	1.3/ -
DREAM (2006)	5269 55 years 59 % female	0 % CAD 0 % DM All had IGT/IFG	Ramipril 15 mg vs. placebo	136/ 83.4	4.3/ 2.7
EUROPA (2003)	12 218 60 years 15 % female	100 % CAD 12 % DM	Perindopril 8 mg vs. placebo	137/ 82	5/ 2
HOPE (2000)	9297 66 years 27 % female	81 % CAD 38 % DM	Ramipril 10 mg vs. placebo	139/ 79	3/ 2*
HOPE-3 (2016)	12 705 66 years 46 % female	0 % CAD 6 % DM	Candesartan/ HCTZ 16/12.5 mg vs. placebo	138.1/ 81.9	6/ 3
Lewis (1993)	409 35 years 47 % female	100 % DM (type 1) All with nephropathy	Captopril 75 mg vs. placebo	138.5/ 85.5	1.5/ 2.5
NAVIGATOR (2010)	9306 64 years 51 % female	24 % CAD 0 % DM 100 % IGT	Valsartan 160 mg vs. placebo	139.7/ 82.6	2.8/ 1.4
PART-2 (2000)	617 61 years 18 % female	68 % CAD (100 % CVD) 9 % DM	Ramipril 5-10 mg vs. placebo	133/ 79	5.5/ 4
PEACE (2004)	8290 64 years 18 % female	100 % CAD 17 % DM	Trandolapril 4 mg vs. placebo	133/ 78	3.0/ 1.2
PHARAO (2008)	1008 62 years 52 % female	6 % CAD 13 % DM	Ramipril 5 mg vs. placebo	134.4/ 83.6	2.8/ 0.9

PREVEND-IT (2004)	864 51 years 35 % female	3 % CAD 3 % DM	Fosinopril 20 mg vs. placebo	130/ 76	3/ 3
Ravid (1998)	194 55 years 51 % female	0 % CAD 100 % DM	Enalapril 10 mg vs. placebo	MAP 97	-/ -
ROADMAP (2011)	4447 58 years 54 % female	25 % CAD 100 % DM	Olmesartan 40 mg vs. placebo	136.5/ 80.5	3.1/ 1.9
SCAT (2000)	460 61 years 11 % female	100 % CAD 11 % DM	Enalapril 10 mg vs. placebo	130/ 77.5	5.2/ 3.3
VA-NEPHRON (2013)	1448 65 years 0.3 % female	23 % CAD 100 % DM with nephro-pathy	Losartan/ lisinopril 100/10-40 mg vs. losartan 100 mg	137.0/ 72.7	1.5/ 1.0

* A sub-study assessing ABPM found larger BP differences between groups during follow-up, indicating potentially underestimated BP differences in the main publication. SBP = systolic blood pressure. DBP = diastolic blood pressure. CAD = coronary artery disease. DM = diabetes mellitus. AF = atrial fibrillation. CKD = chronic kidney disease. IGT = impaired glucose tolerance. IFG = impaired fasting glucose. HCTZ = hydrochlorothiazide. MAP = mean arterial pressure.

Table 2. Secondary outcomes

		Primary prevention trials			Coronary artery disease trials		
		Trials/ participants/ events (n)	RR (95 % CI)	I^2 (%)	Trials/ participants/ events (n)	RR (95 % CI)	I^2 (%)
Efficacy outcomes	Cardiovascular mortality	8 / 49 685 / 2390	1.07 (0.95-1.21)	27.3	5 / 37 589 / 1802	0.86 (0.74-1.00)	55.7
	Myocardial infarction	8 / 46 682 / 1092	1.03 (0.91-1.15)	0.0	5 / 29 893 / 2367	0.83 (0.72-0.97)	60.0
	Stroke	9 / 47 546 / 1536	0.89 (0.73-1.09)	52.9	6 / 38 049 / 943	0.79 (0.66-0.94)	36.6
	Heart failure	6 / 44 881 / 1903	0.90 (0.81-1.00)	17.7	5 / 37 589 / 957	0.76 (0.67-0.86)	0.0
Safety outcomes	Hypotension-related AEs	6 / 44 058 / 5141	1.71 (1.32-2.22)	90.3	3 / 28 817 / 793	1.63 (1.01-2.63)	85.9
	Renal impairment	8 / 49 627 / 992	1.20 (0.93-1.55)	71.6	1 / 12 215 / 36	1.25 (0.65-2.41)	-

RR = relative risk. CI = confidence interval. AEs = adverse events

Figure legends

Figure 1 – Treatment effect on primary outcomes in primary prevention. CI = confidence interval.

Figure 2 – Treatment effect on primary outcomes in coronary artery disease trials. CI = confidence interval.

Figure 1

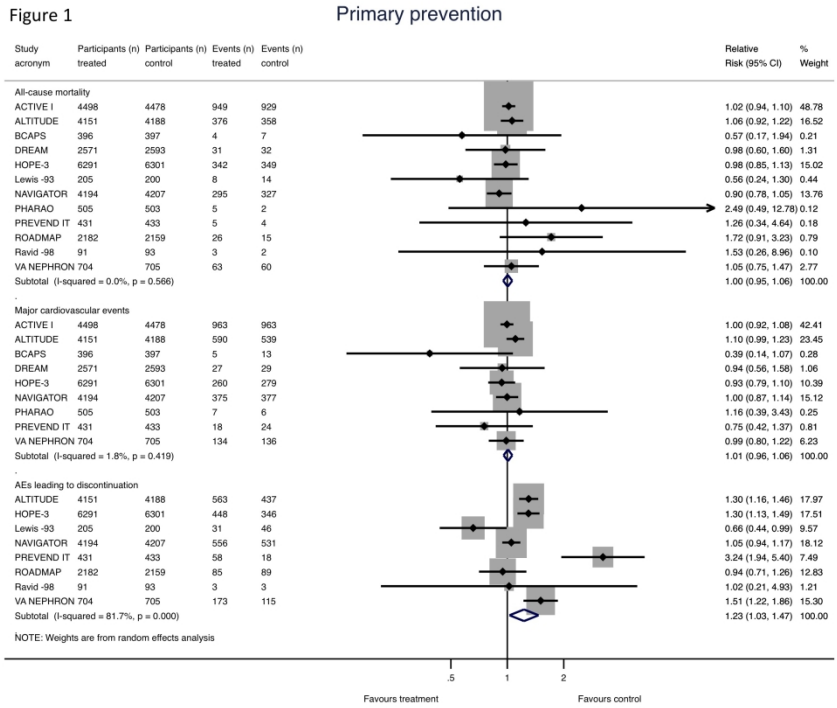

Figure 1 – Treatment effect on primary outcomes in primary prevention. CI = confidence interval.

1057x793mm (72 x 72 DPI)

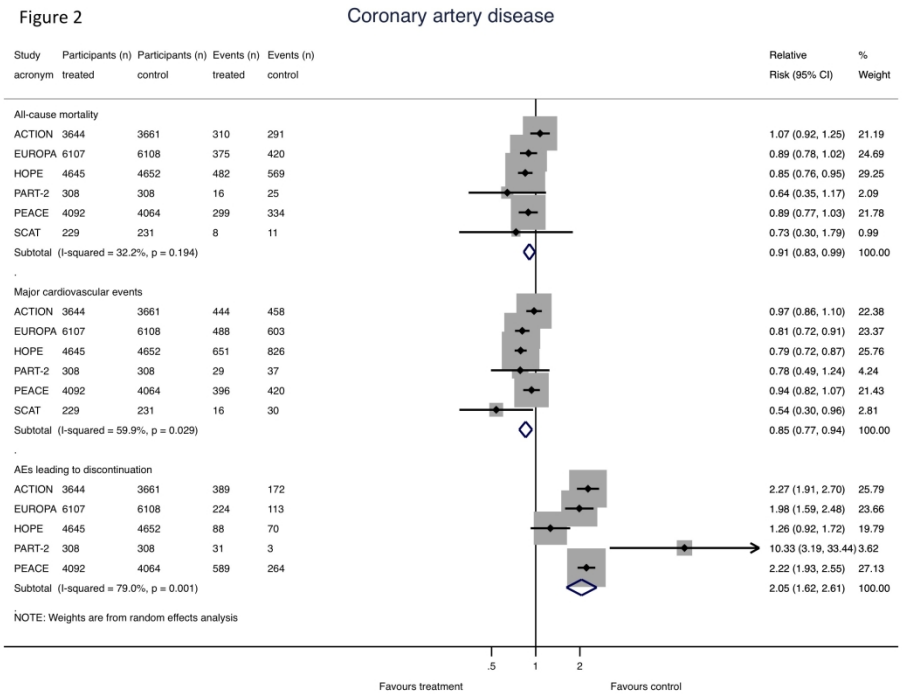

Figure 2 – Treatment effect on primary outcomes in coronary artery disease trials. CI = confidence interval.

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ONLINE SUPPLEMENT

Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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eMethods - Search strategy for previous systematic review

The previous systematic review used a two-stage approach. First, we searched for systematic reviews of randomized controlled trials assessing antihypertensive treatment. All trials included in any previous systematic review were judged in full text against our eligibility criteria. We then performed an additional search for randomized controlled trials published after the latest previous search (with a few months overlap to account for time lag in indexing).

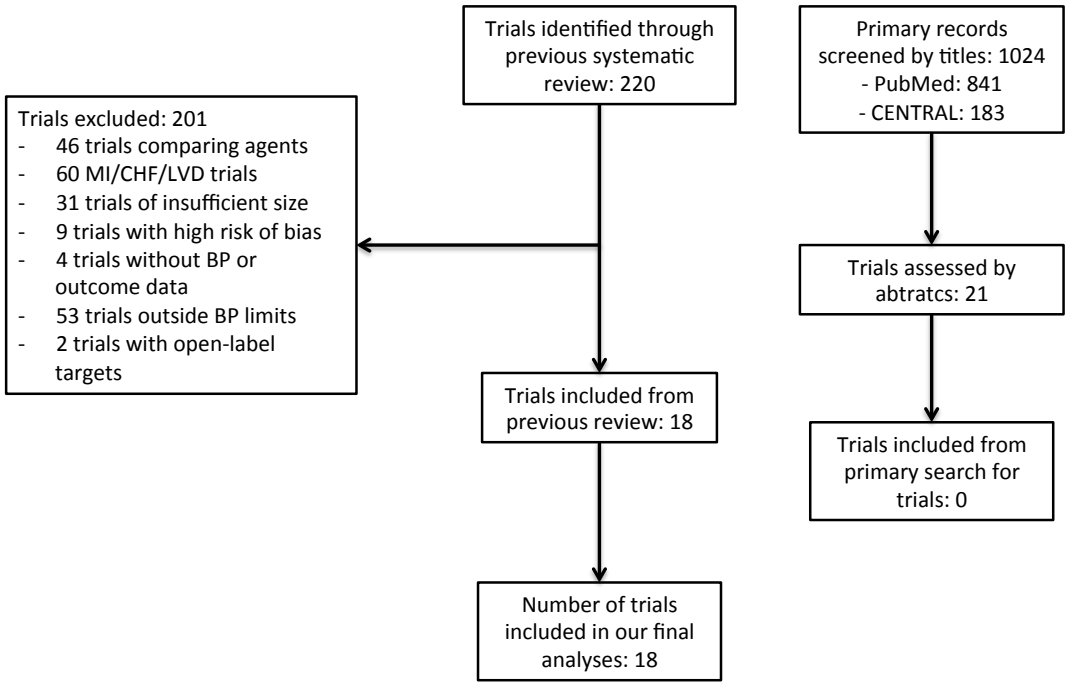
Search strategy systematic reviews
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke) in all databases, adding the filter for meta-analyses in PubMed.

The titles of the retrieved articles were browsed to identify reviews concerning the effect of BP lowering on death, cardiovascular events and renal disease. Reviews concerning treatment of other conditions, effects of specific agents, or the effect of BP lowering on other outcomes, were discarded. All randomized controlled trials included in any of the reviews deemed relevant were retrieved in full text and judged according to the above eligibility criteria.

Search strategy for randomized controlled trials
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke), adding ("2015/11/01"[Date – Publication] : "3000"[Date – Publication]) to the PubMed search and limiting the CENTRAL search to 2015-2017.

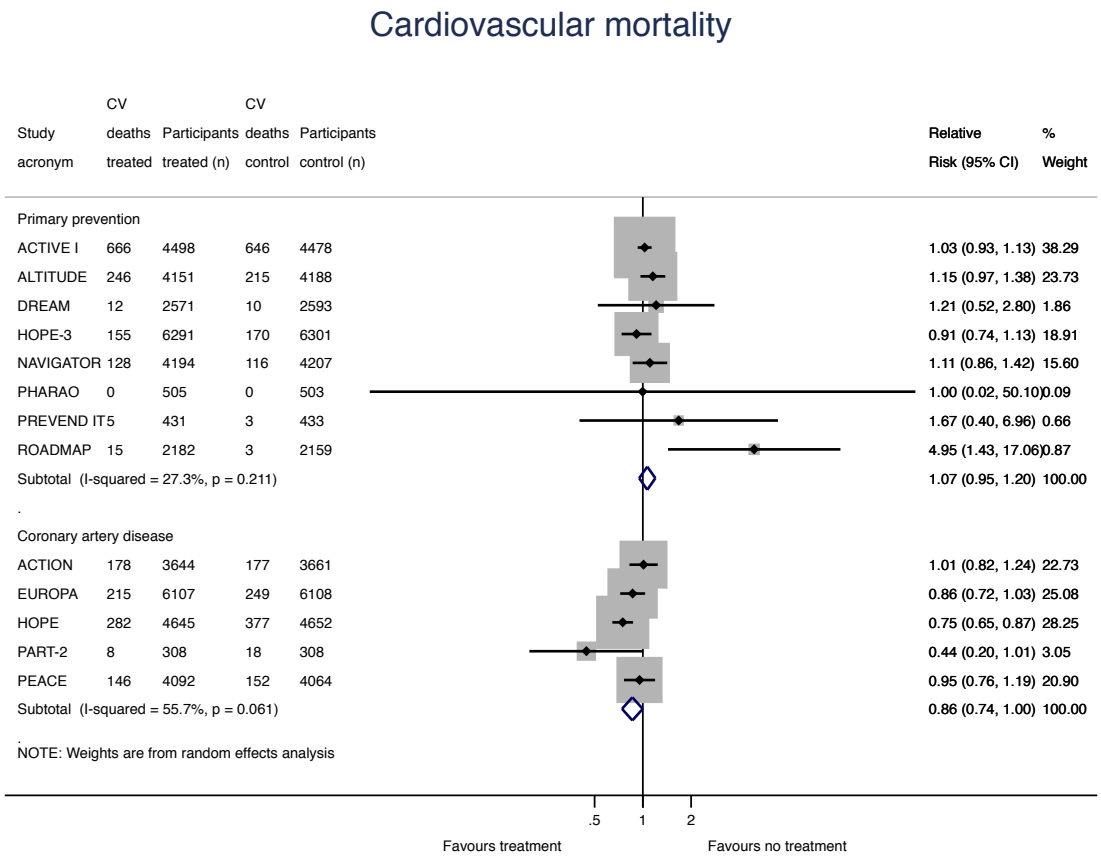
We also performed an alternative PubMed search, using the phrase (("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND ("2015/11/01"[Date - Publication] : "3000"[Date - Publication])) with RCT filter.

eFigure 1 - PRISMA flow chart



CENTRAL = Cochrane Central Register for Controlled Trials. MI = myocardial infarction. CHF = congestive heart failure. LVD = left ventricular dysfunction. BP = blood pressure.

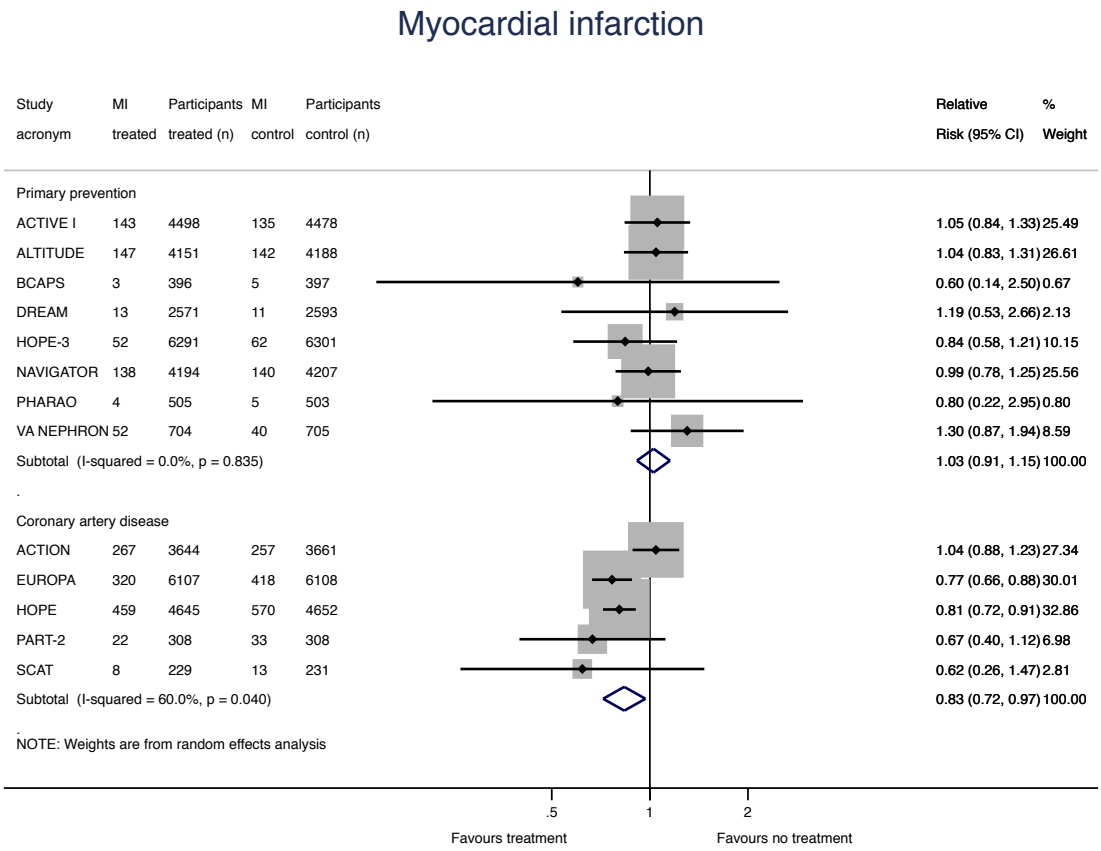
eFigure 2 – Forest plot for cardiovascular mortality



CV = cardiovascular.

Random-effects metaregression for interaction (p=0.047)

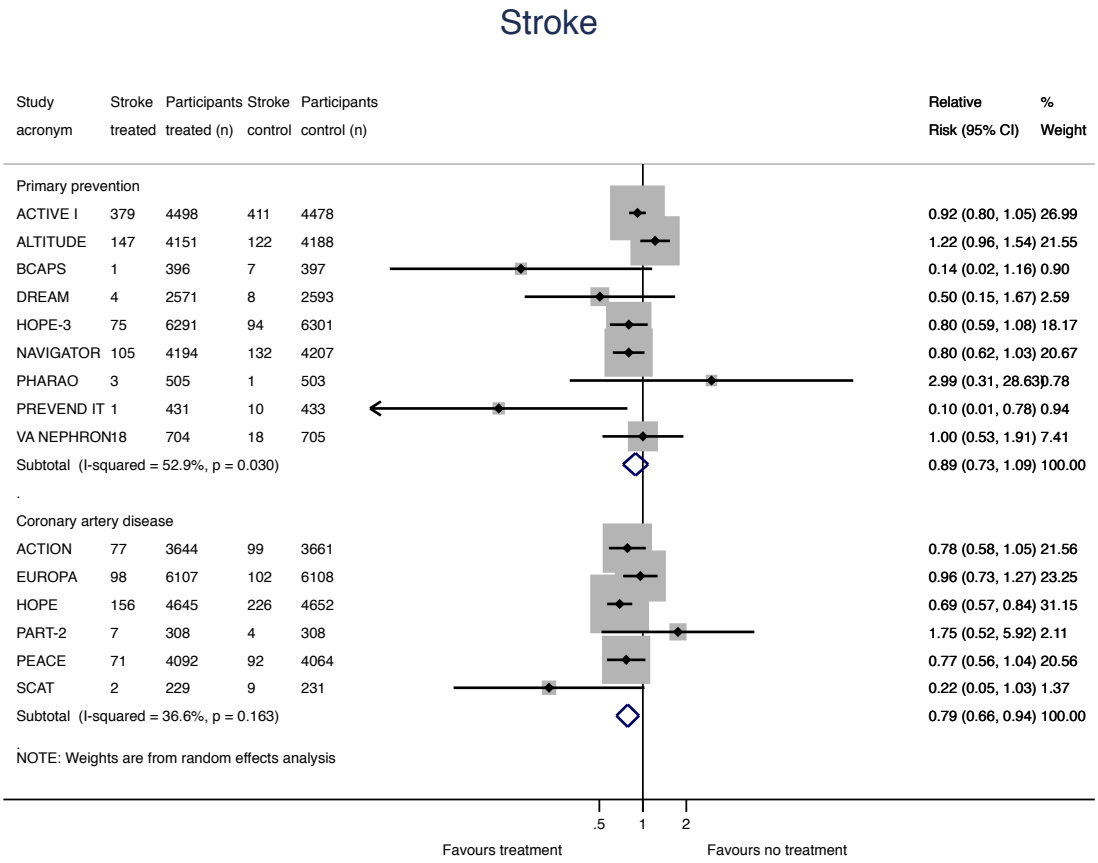
eFigure 3 – forest plot for myocardial infarction



MI = myocardial infarction.

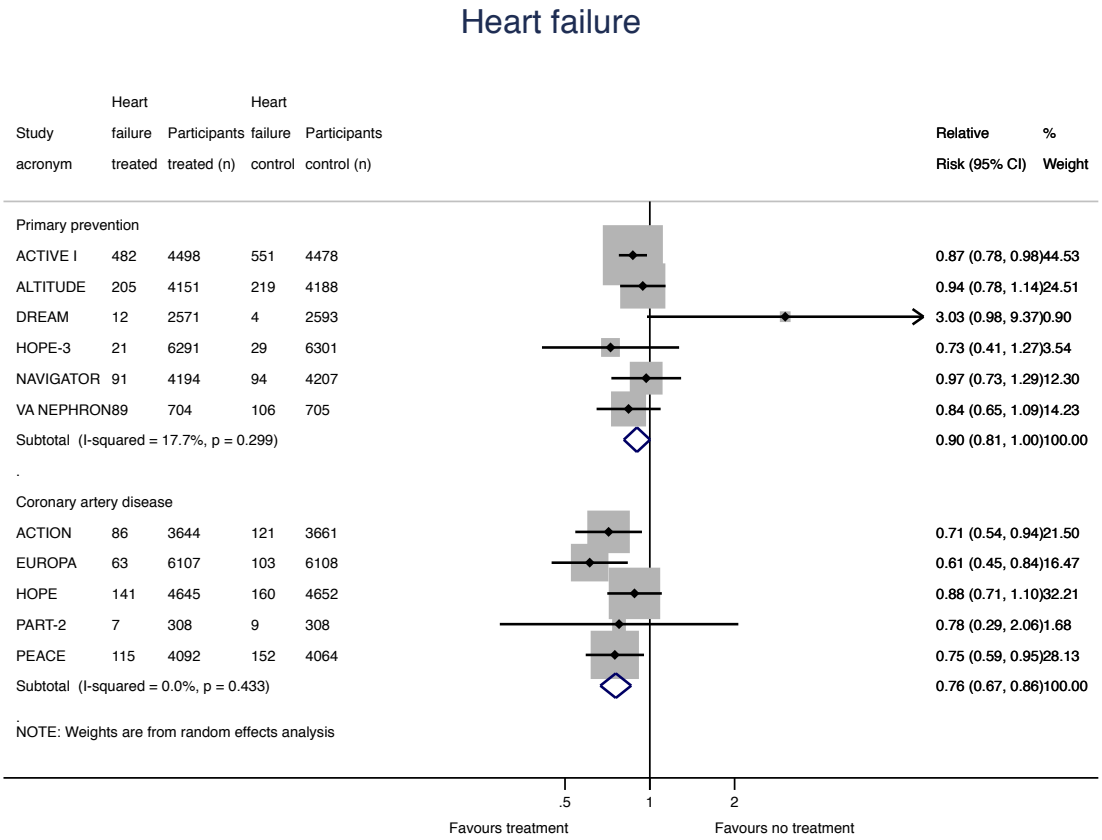
Random-effects metaregression for interaction (p=0.061)

eFigure 4 – forest plot for stroke



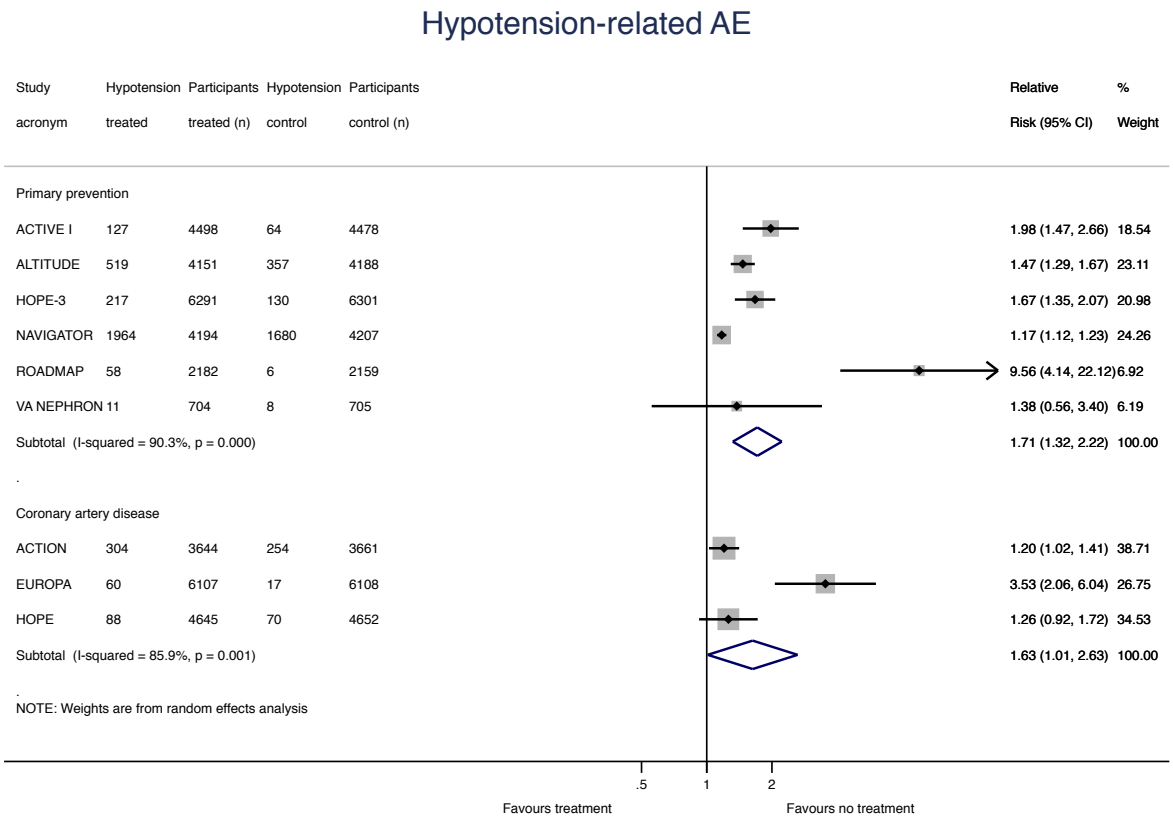
Random-effects metaregression for interaction (p=0.329)

eFigure 5 – forest plot for heart failure



Random-effects metaregression for interaction (p=0.072)

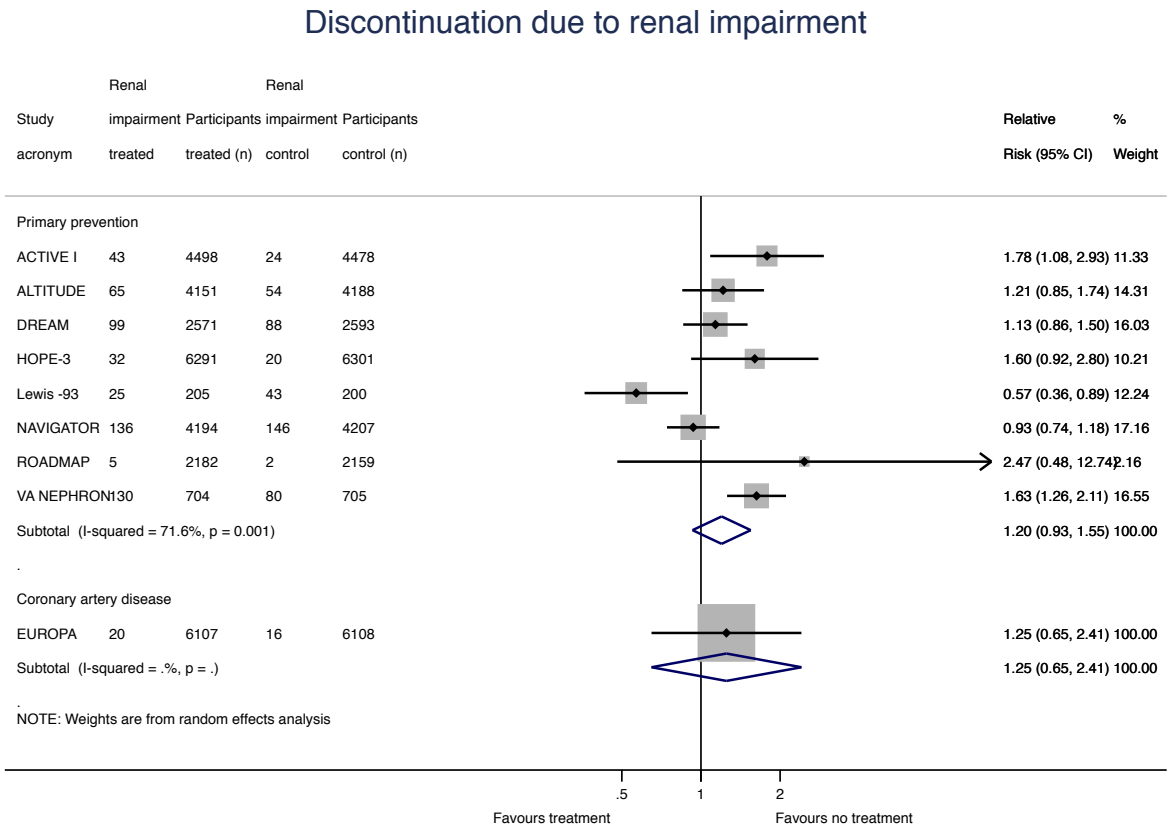
eFigure 6 – forest plot for hypotension-related AEs



AEs = adverse events

Random-effects metaregression for interaction (p=0.798)

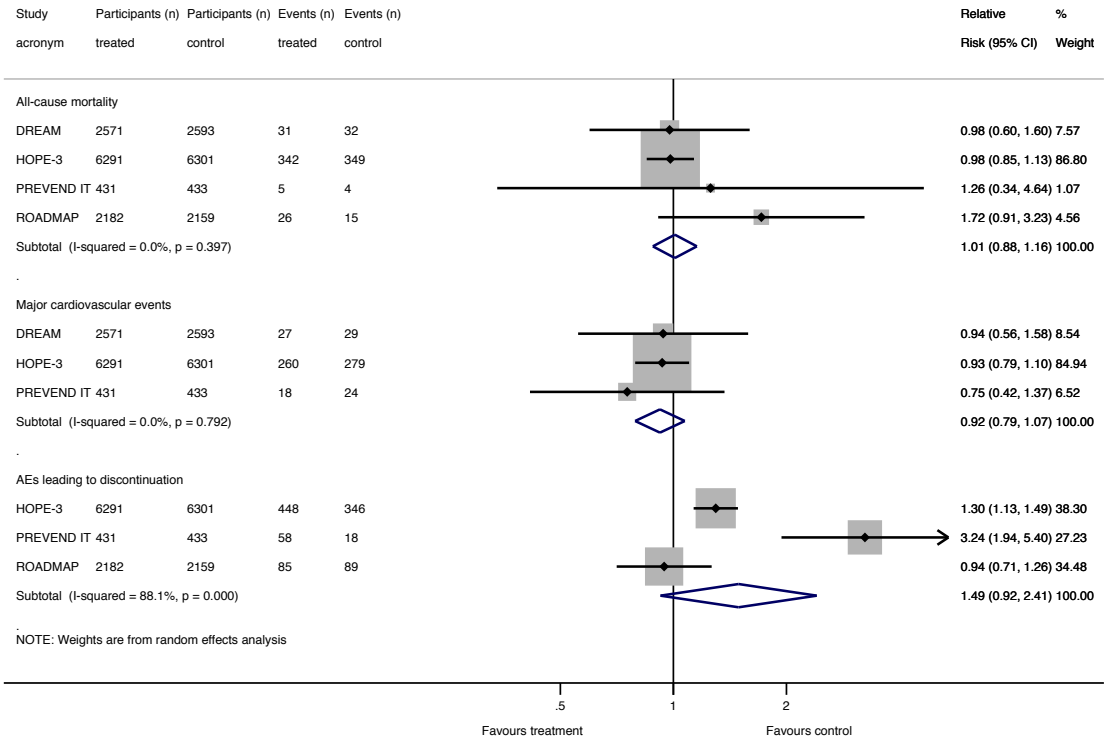
eFigure 7 – forest plot for renal impairment



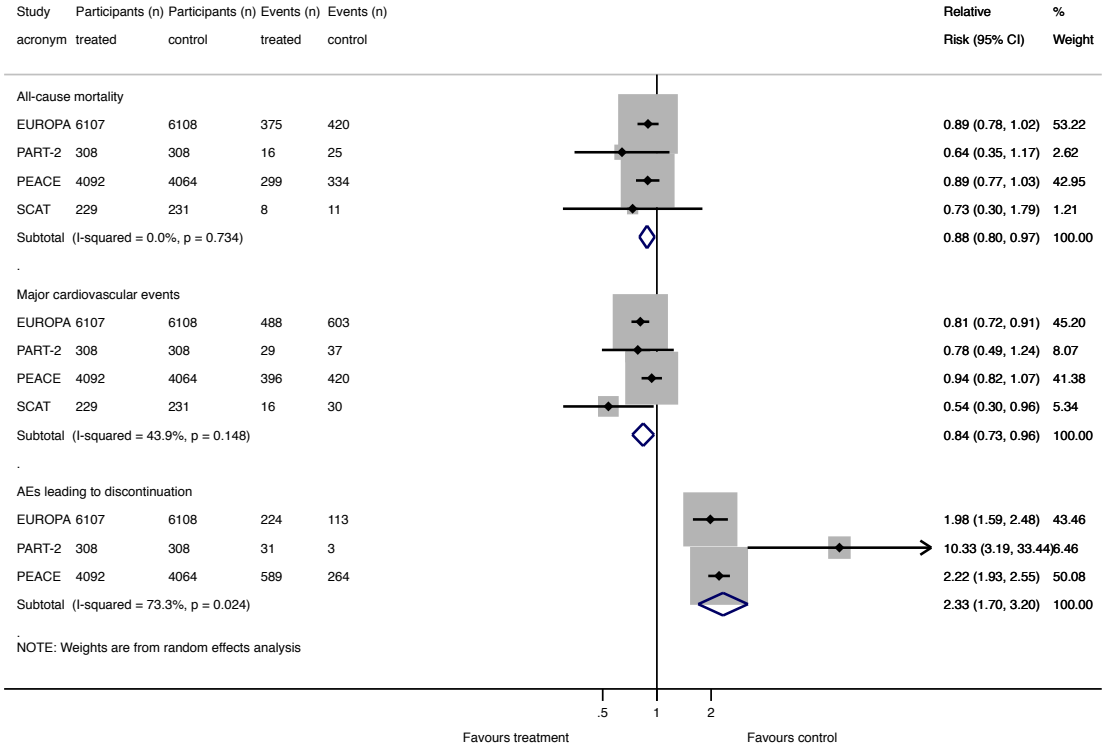
Random-effects metaregression for interaction (p=0.936)

eFigure 8 – Sensitivity analysis excluding trials not reaching < 130 mm Hg

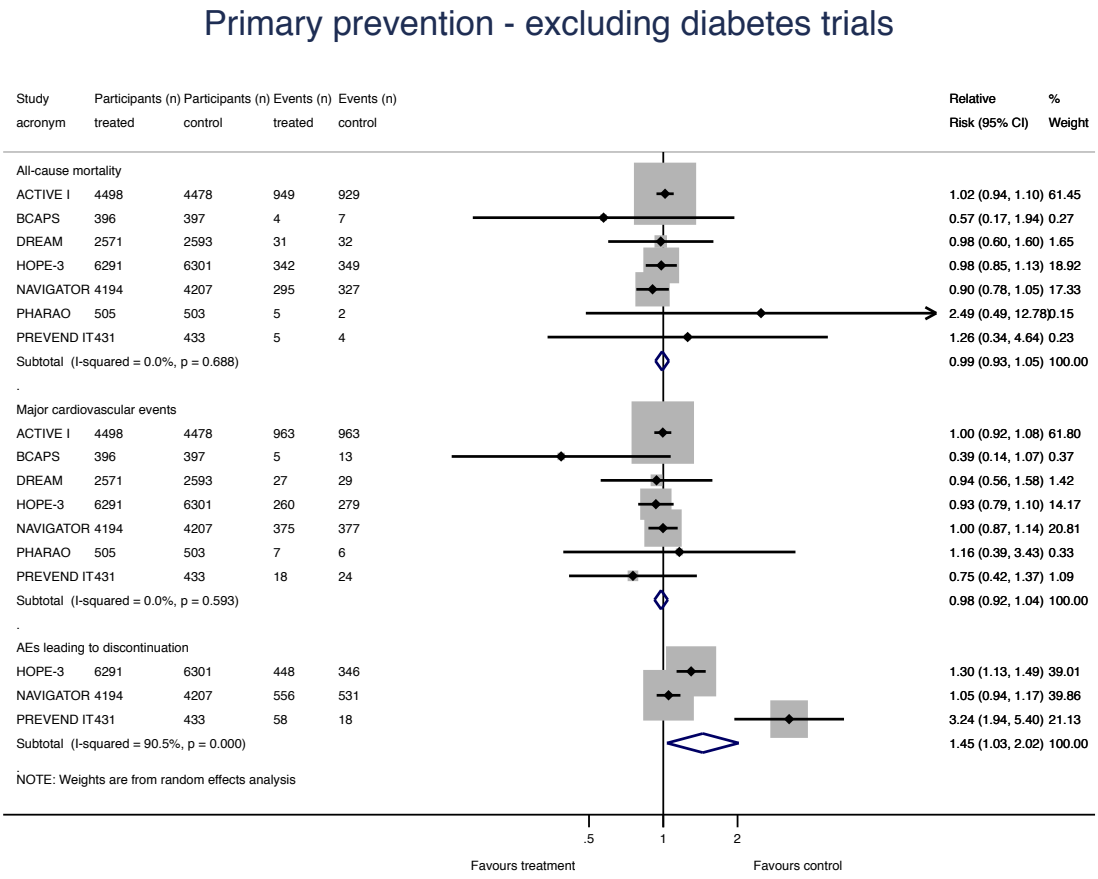
Primary prevention - restricted to trials reaching < 130 mm Hg



Coronary artery disease - restricted to trials reaching < 130 mm hg

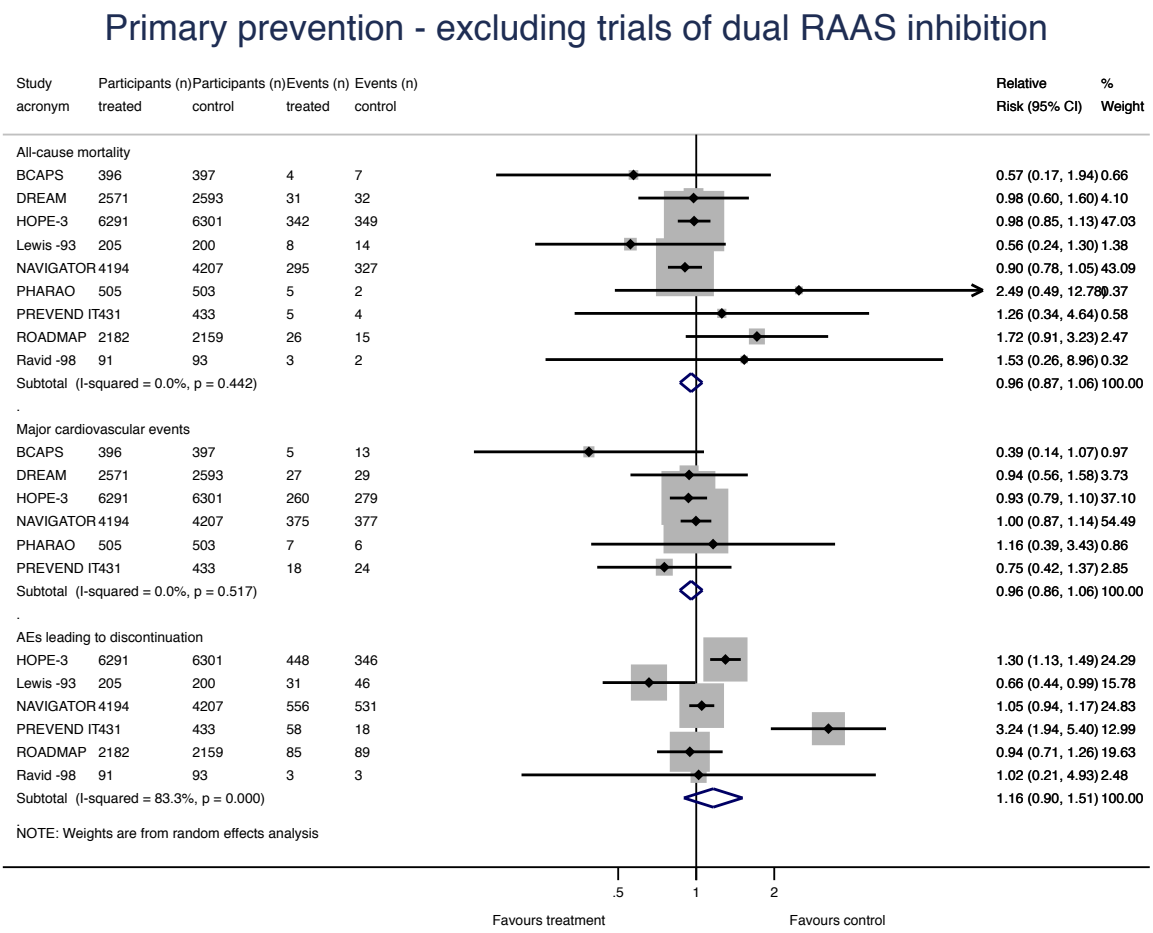


eFigure 9 – sensitivity analysis excluding trials in people with diabetes



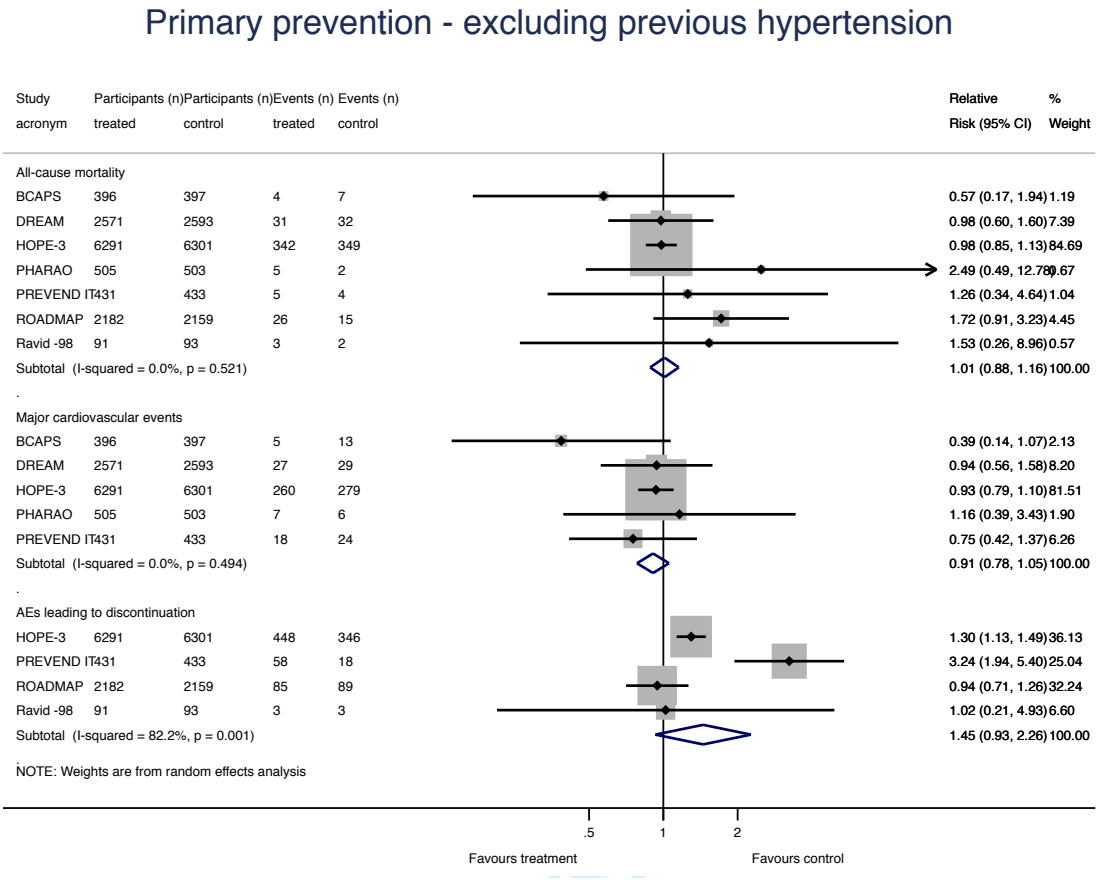
Note: None of CAD trials were primarily in people with diabetes. Hence, no sensitivity analysis was performed.

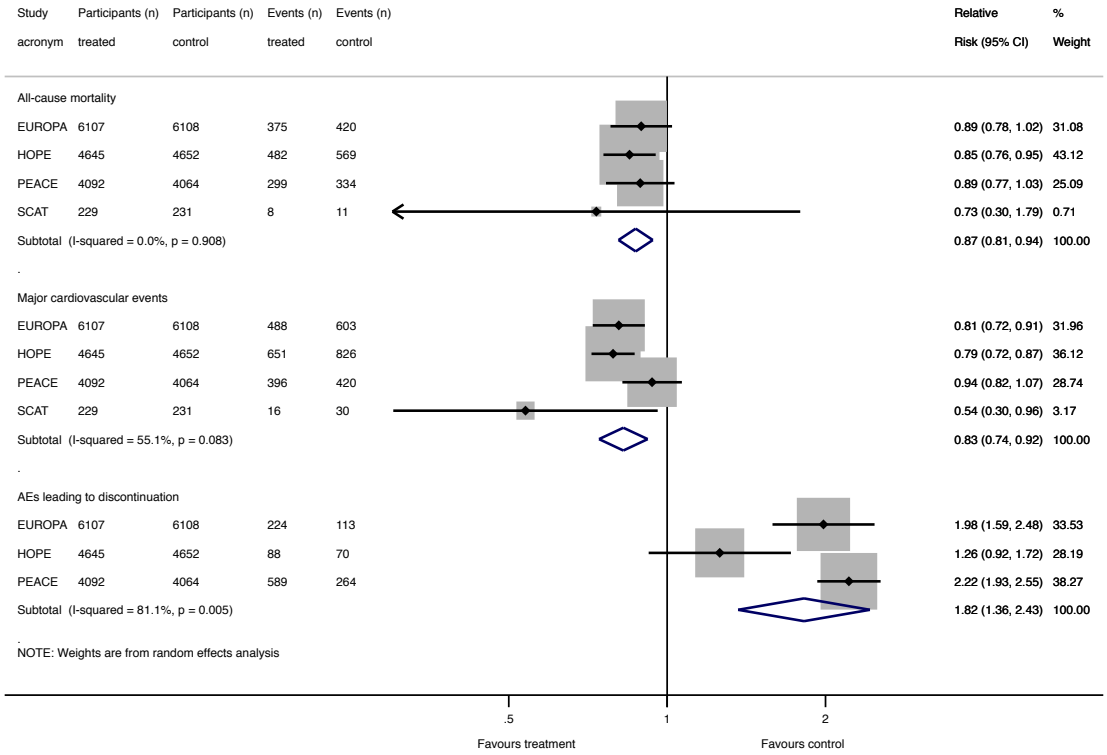
eFigure 10 – sensitivity analysis excluding trials of dual RAAS-inhibition



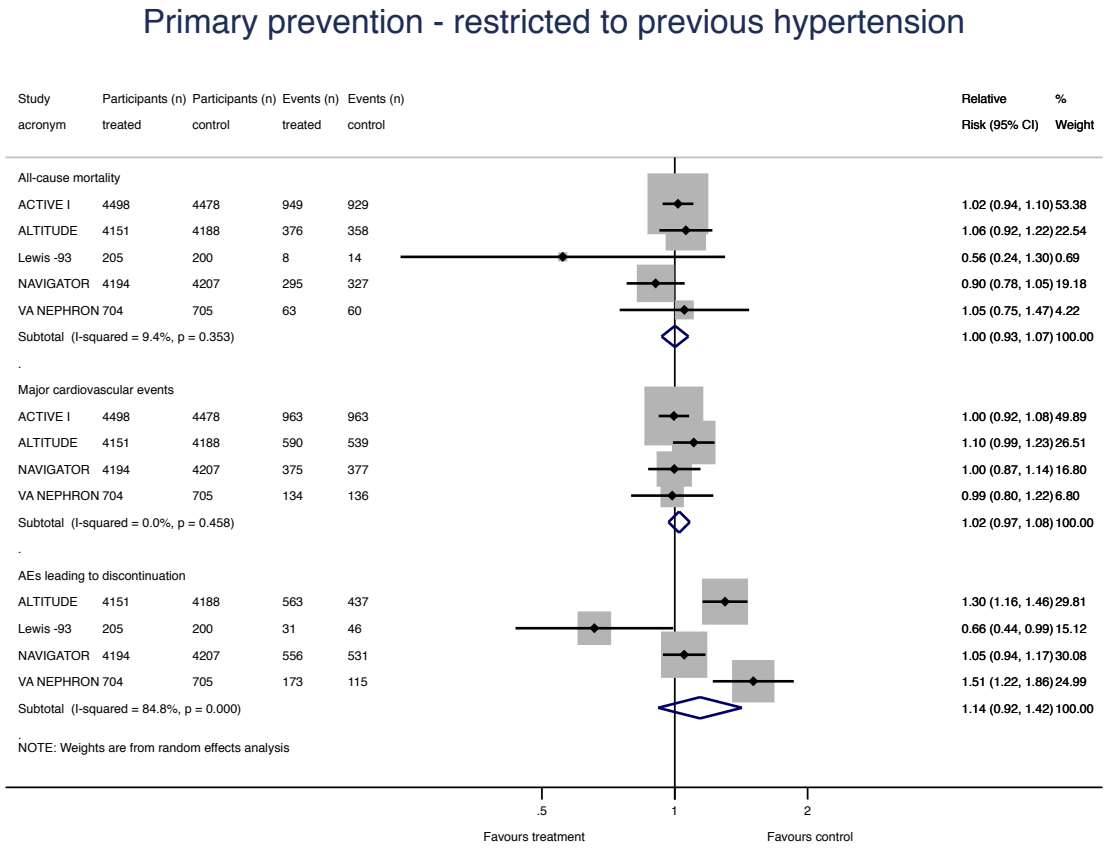
Note: None of CAD trials were testing dual RAAS inhibition. Hence, no sensitivity analysis was performed.

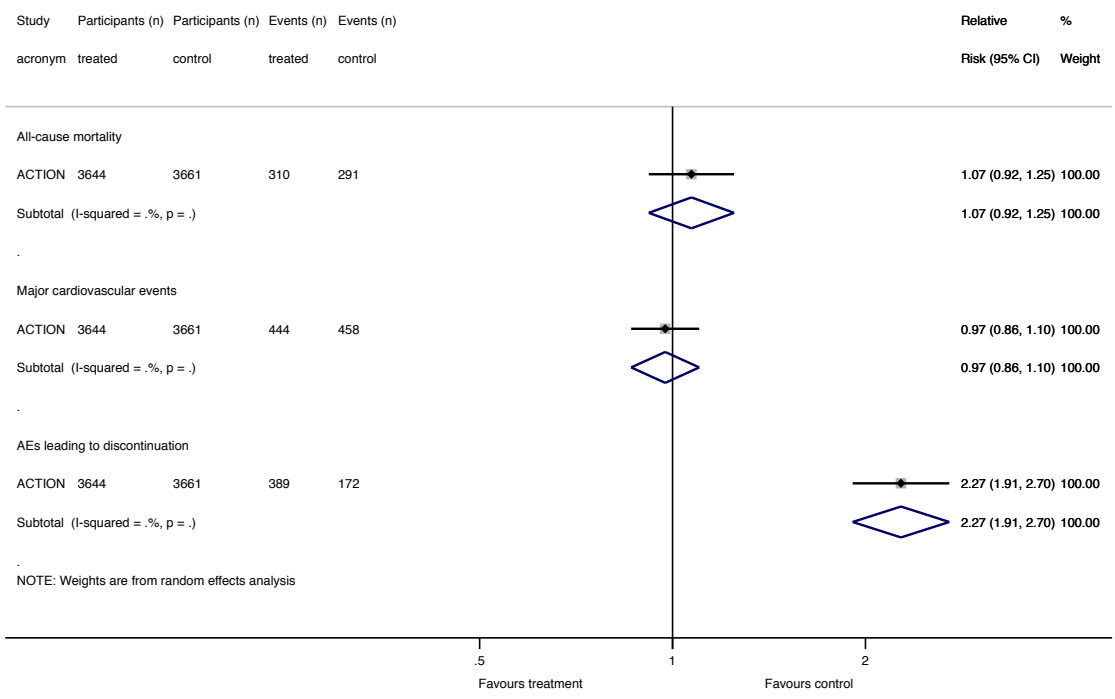
eFigure 11 – sensitivity analysis excluding trials in people with hypertension



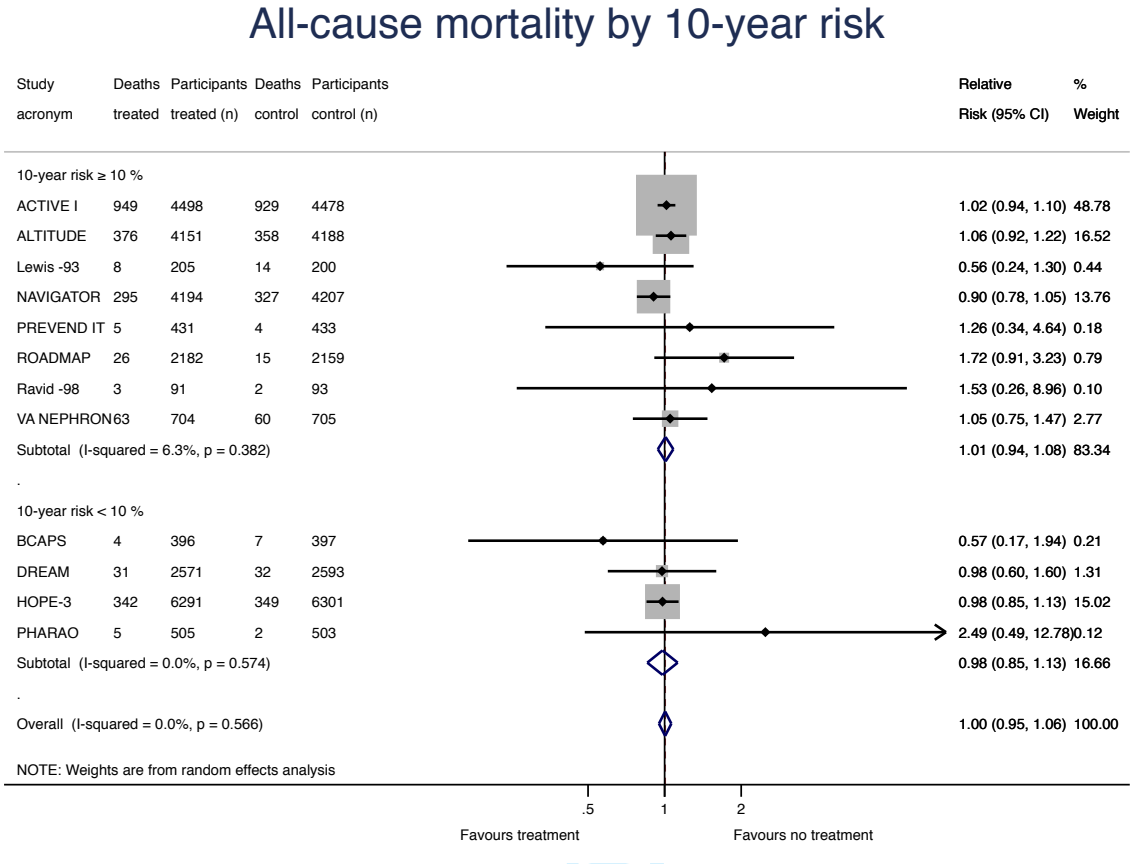


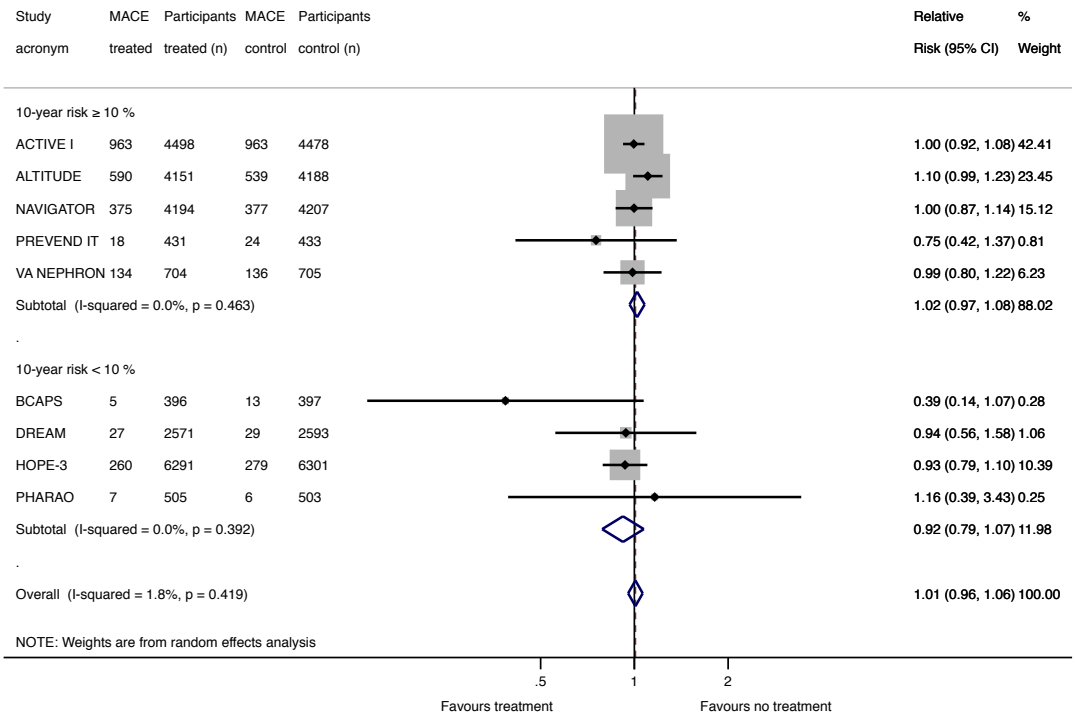
eFigure 12 – sensitivity analysis restricted to trials in people with hypertension

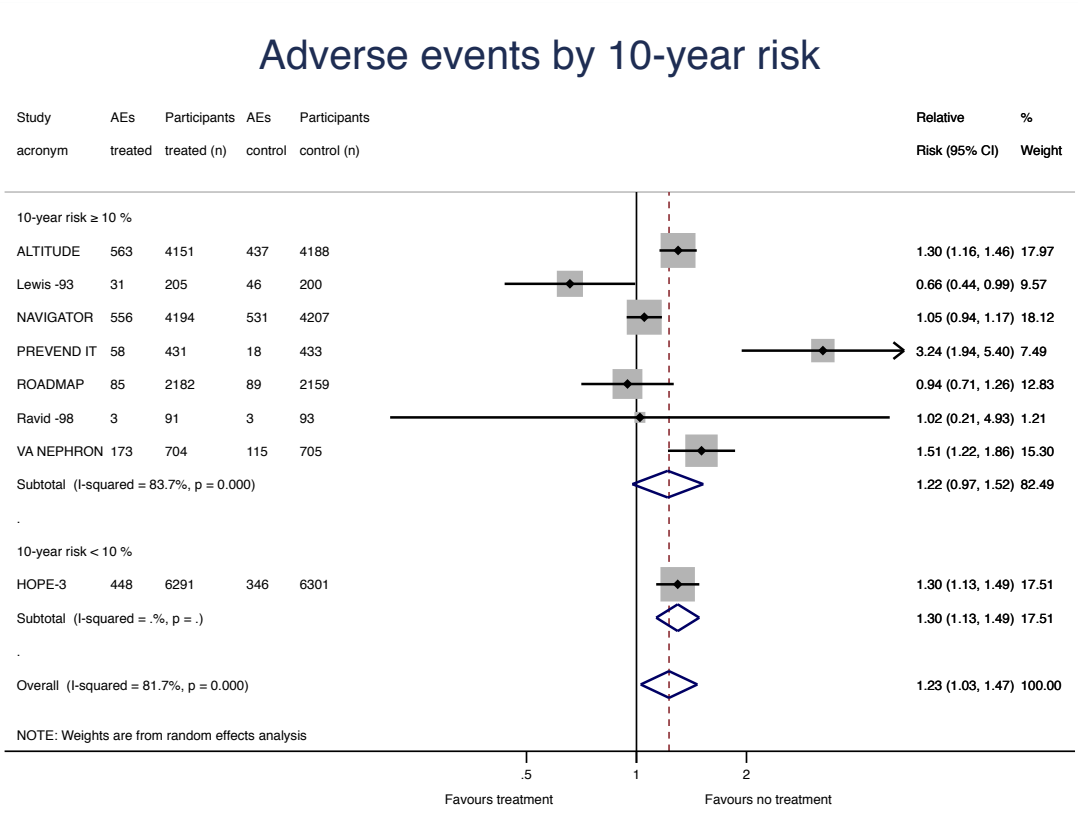




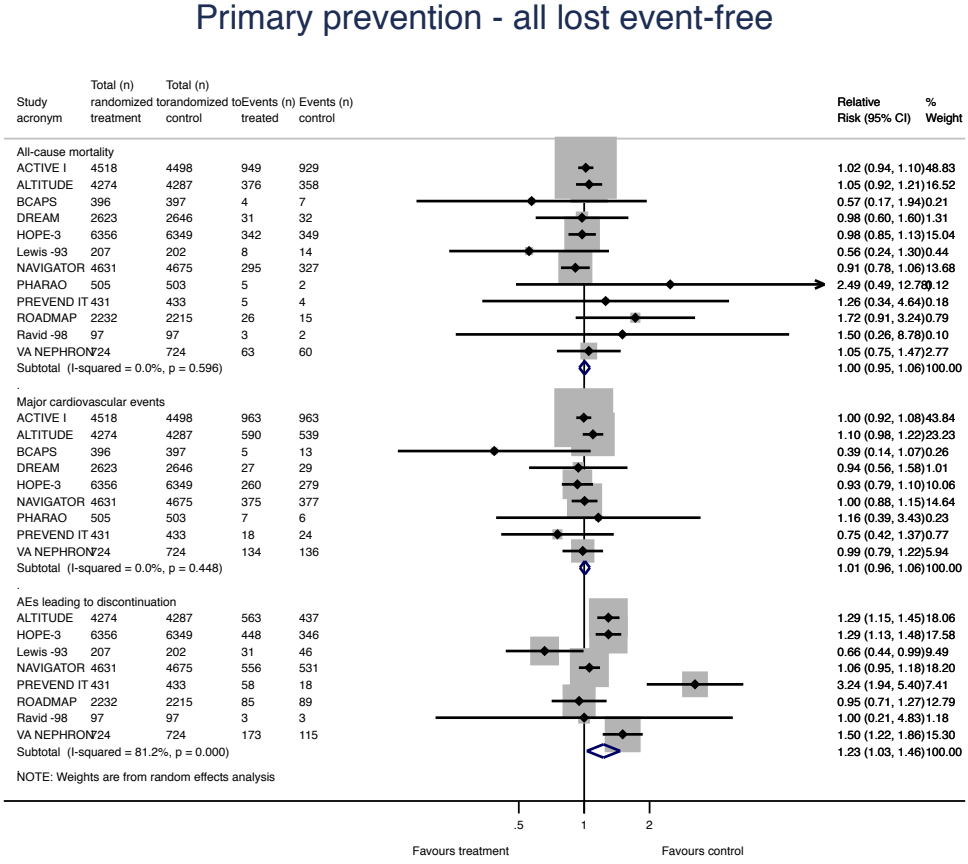
eFigure 13 – Primary preventive trials stratified by 10-year cardiovascular risk

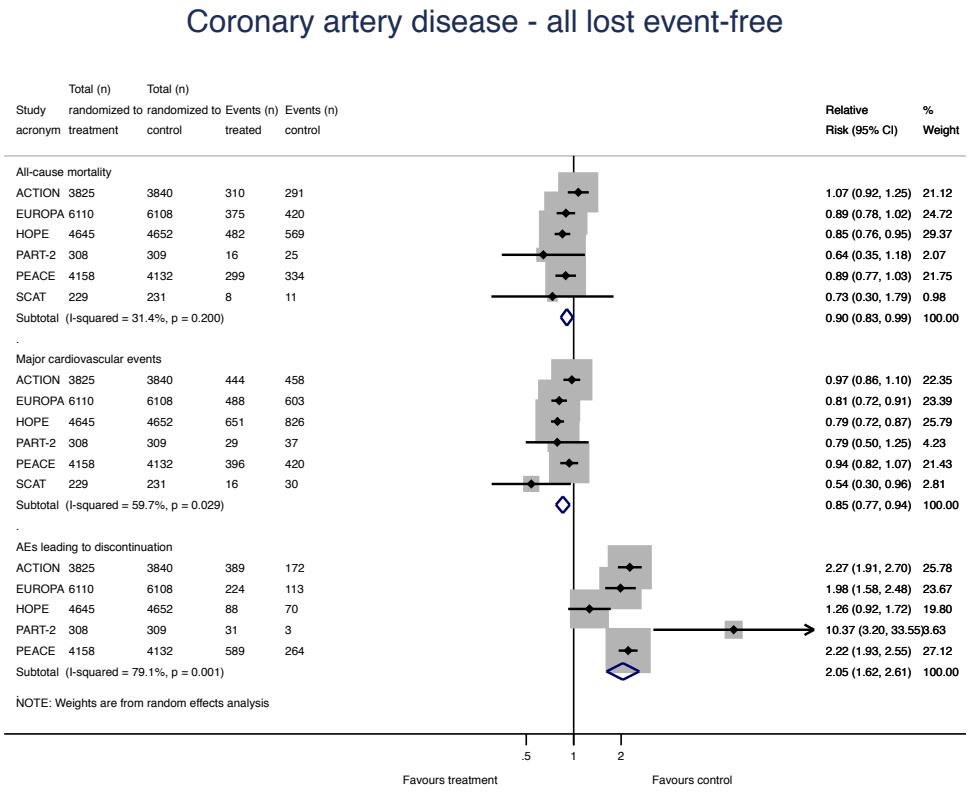




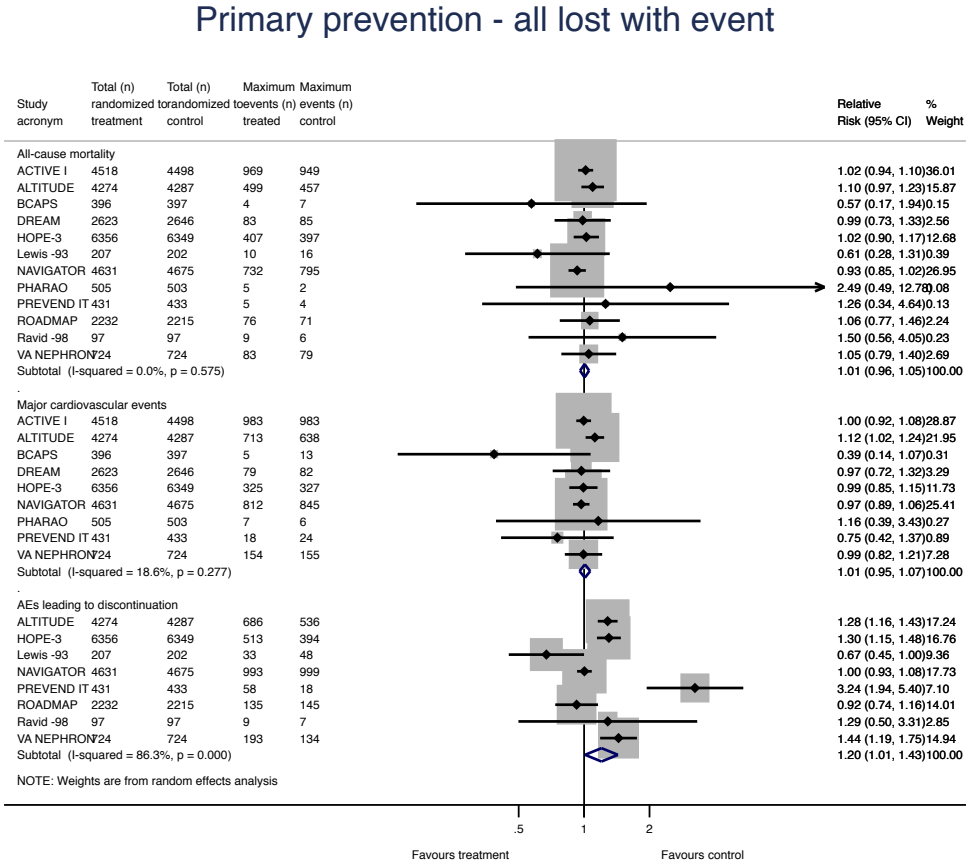


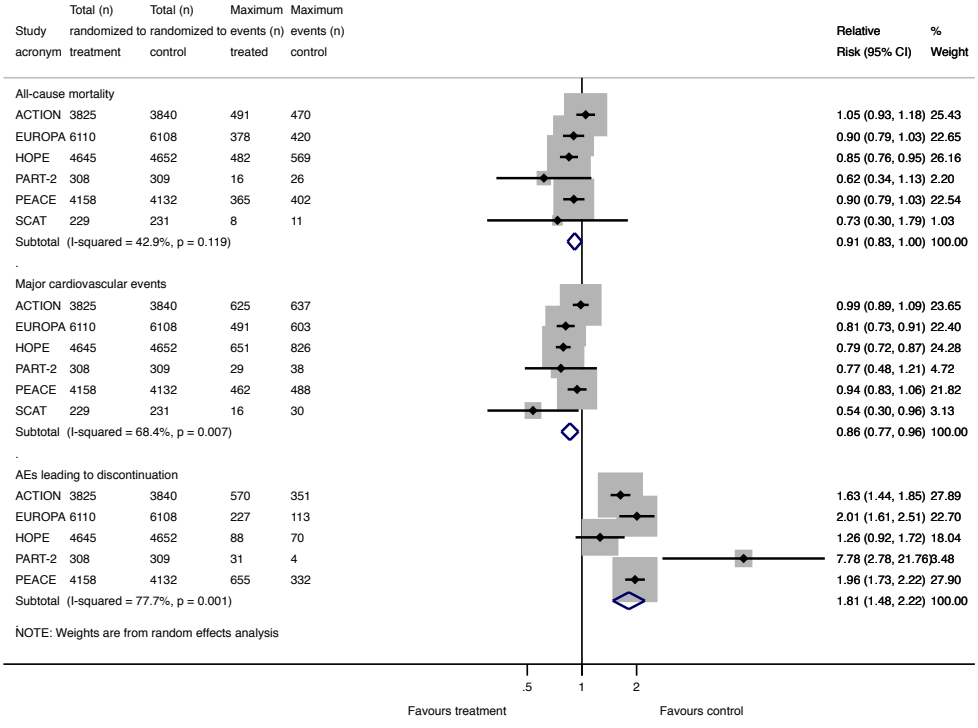
eFigure 14 - Lost to follow-up imputed as event-free



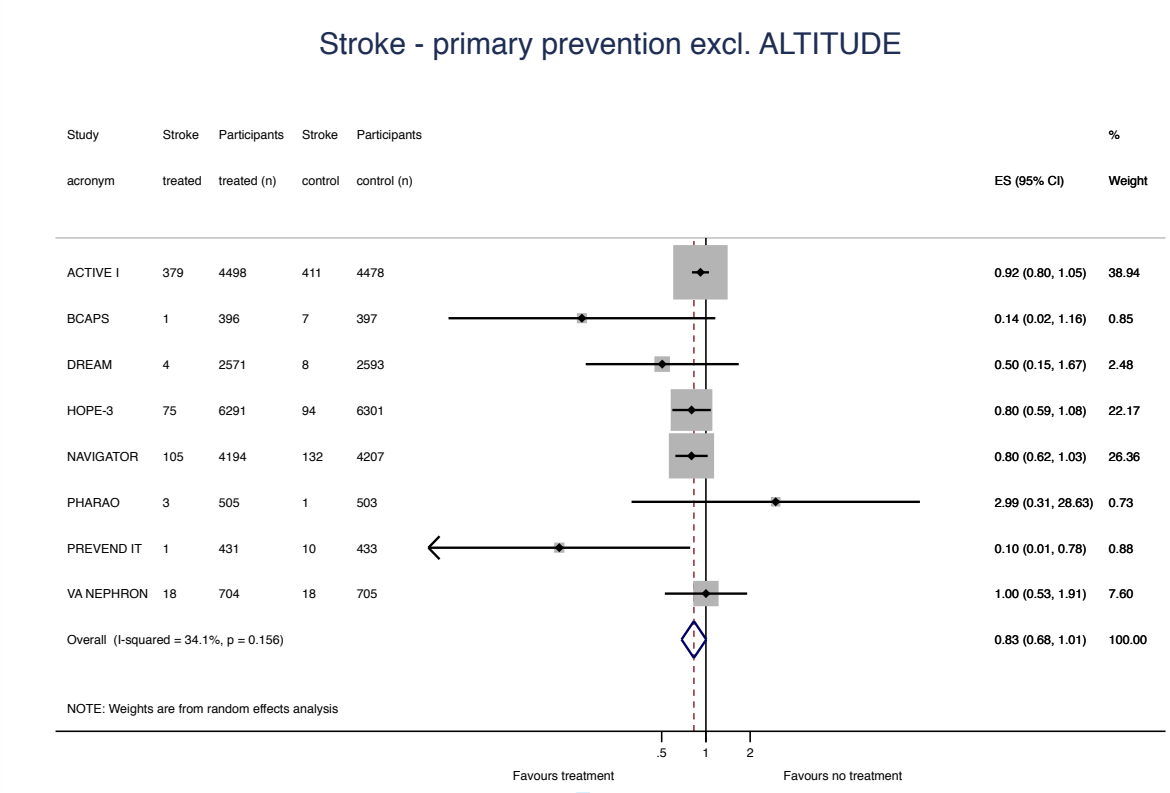


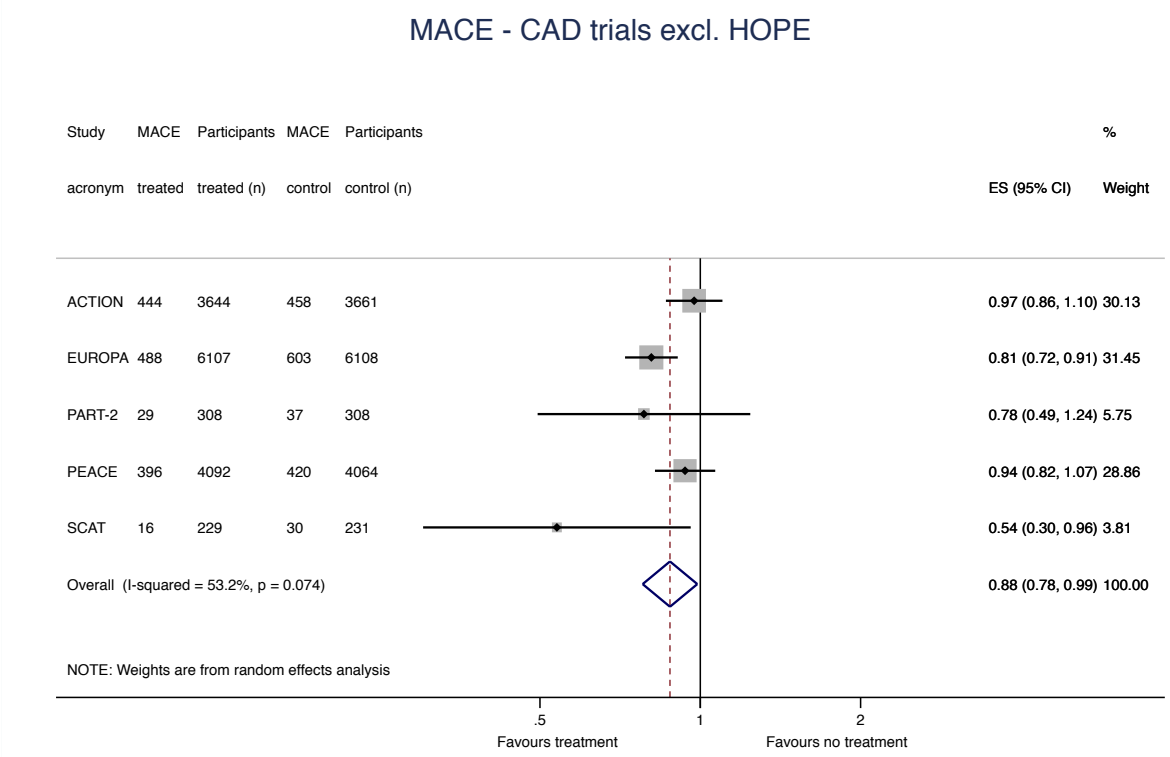
eFigure 15 - lost to follow-up imputed as having an event



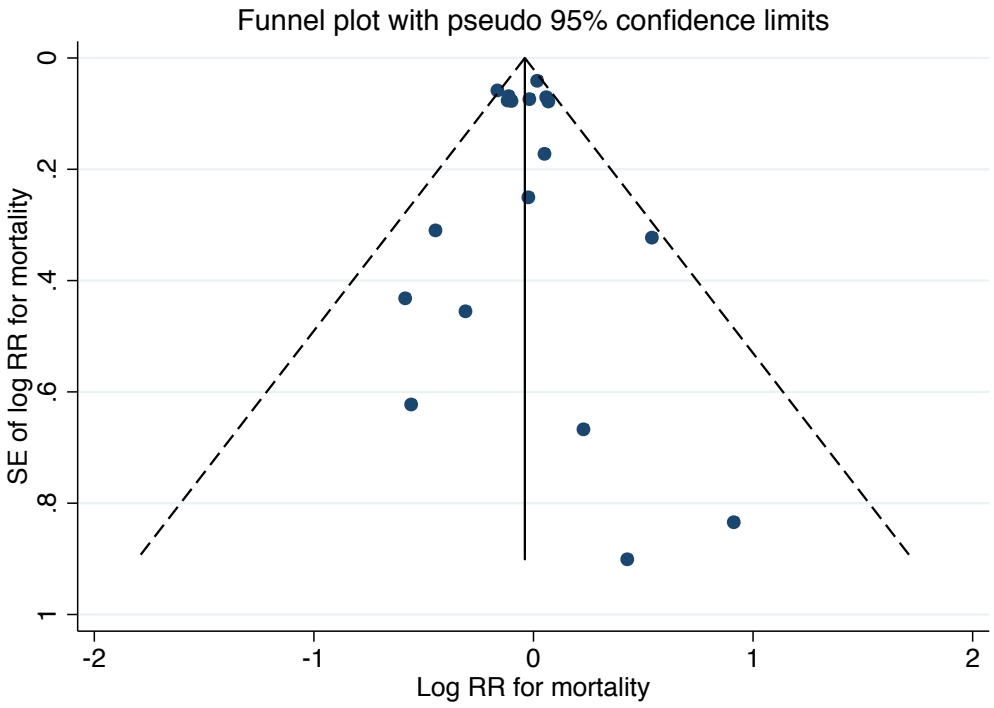


eFigure 16 - Ad hoc sensitivity analyses based on risk of bias assessment



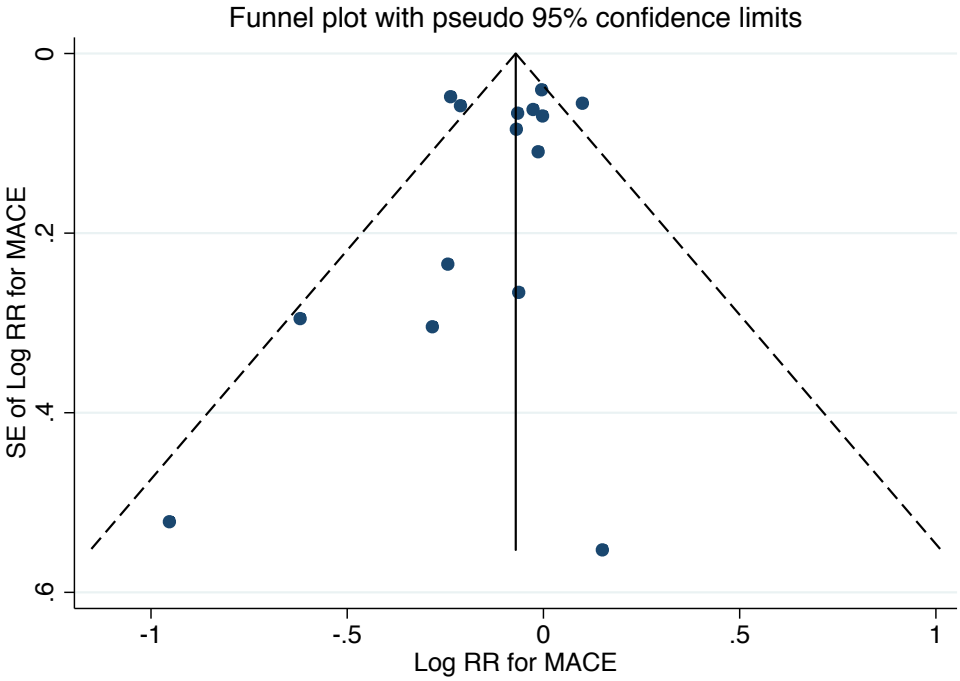


eFigure 17 – Funnel plot for all-cause mortality



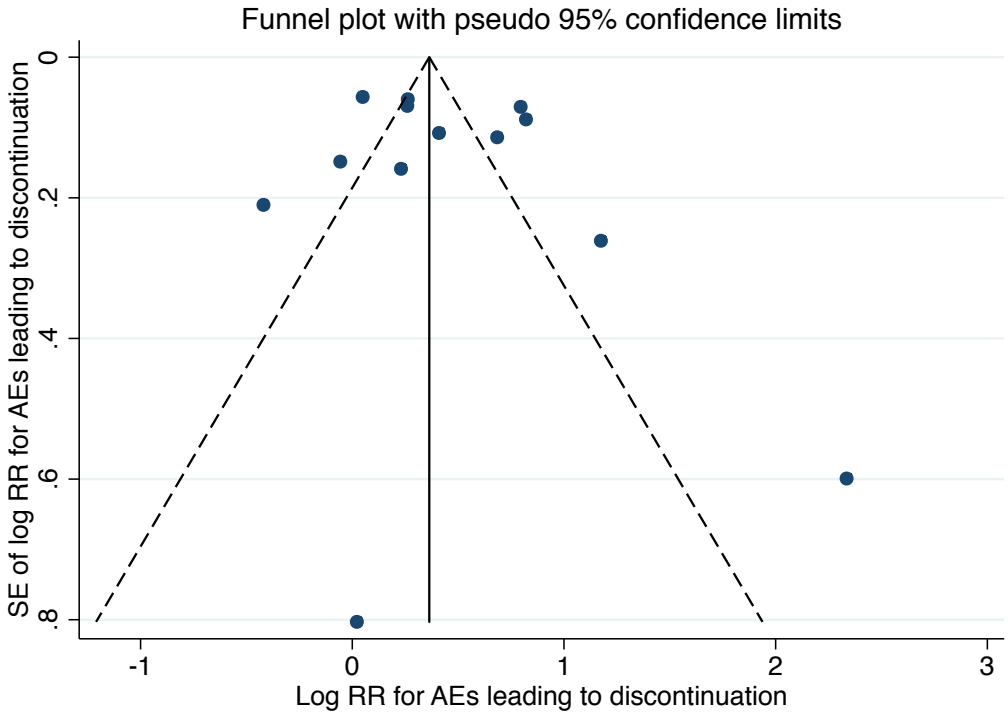
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.938

eFigure 18 – Funnel plot for major cardiovascular events



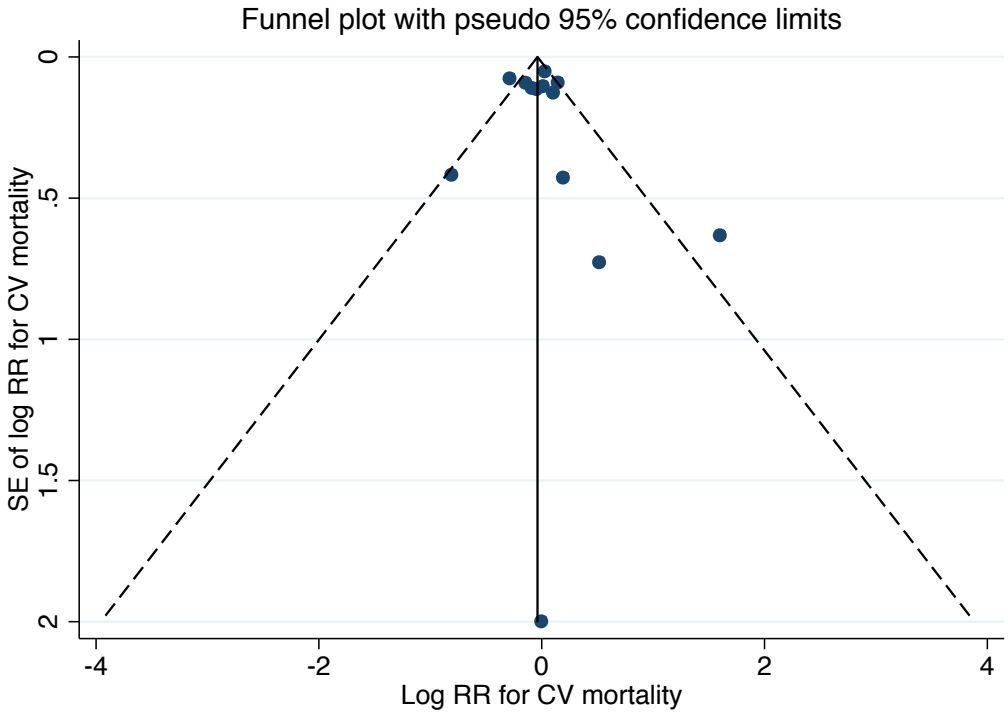
RR = relative risk. SE = standard error. MACE = major cardiovascular events.
Harbord's test for small-study effects p = 0.410

eFigure 19 – Funnel plot for adverse events leading to discontinuation



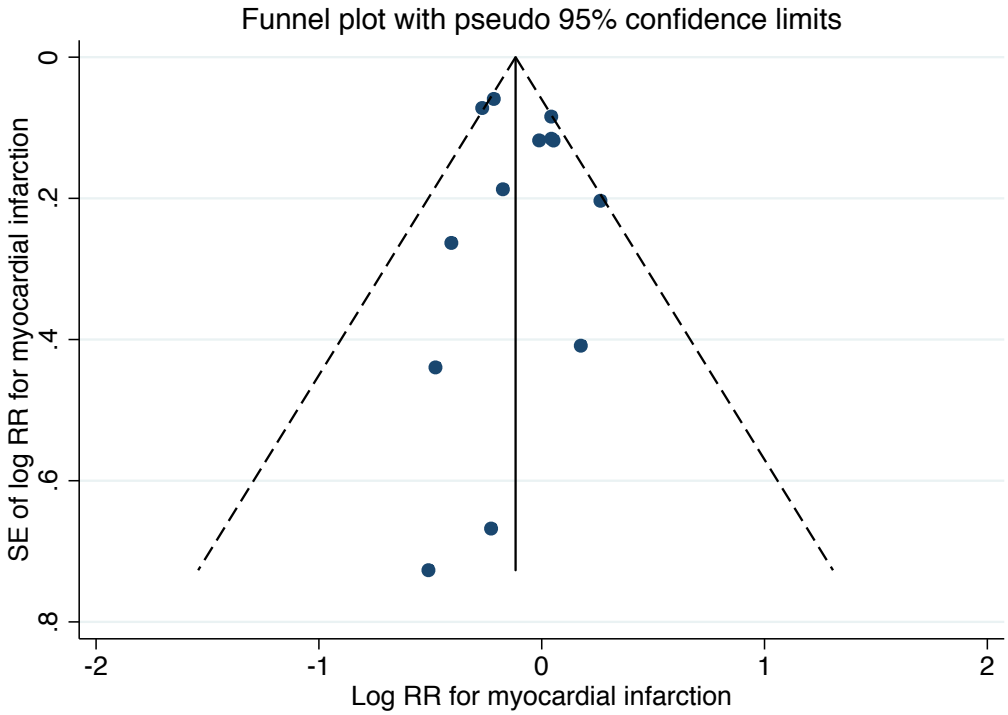
RR = relative risk. SE = standard error. AEs = adverse events.
Harbord's test for small-study effects p = 0.712

eFigure 20 – Funnel plot for cardiovascular mortality



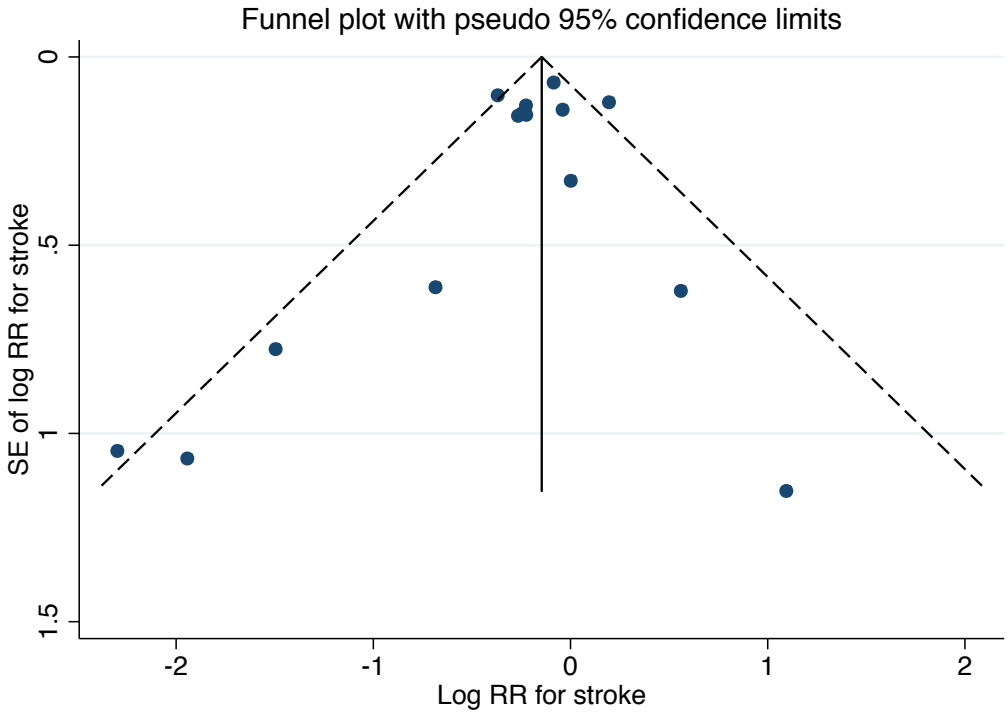
RR = relative risk. SE = standard error. CV = cardiovascular.
Harbord's test for small-study effects p = 0.507

eFigure 21 – Funnel plot for myocardial infarction



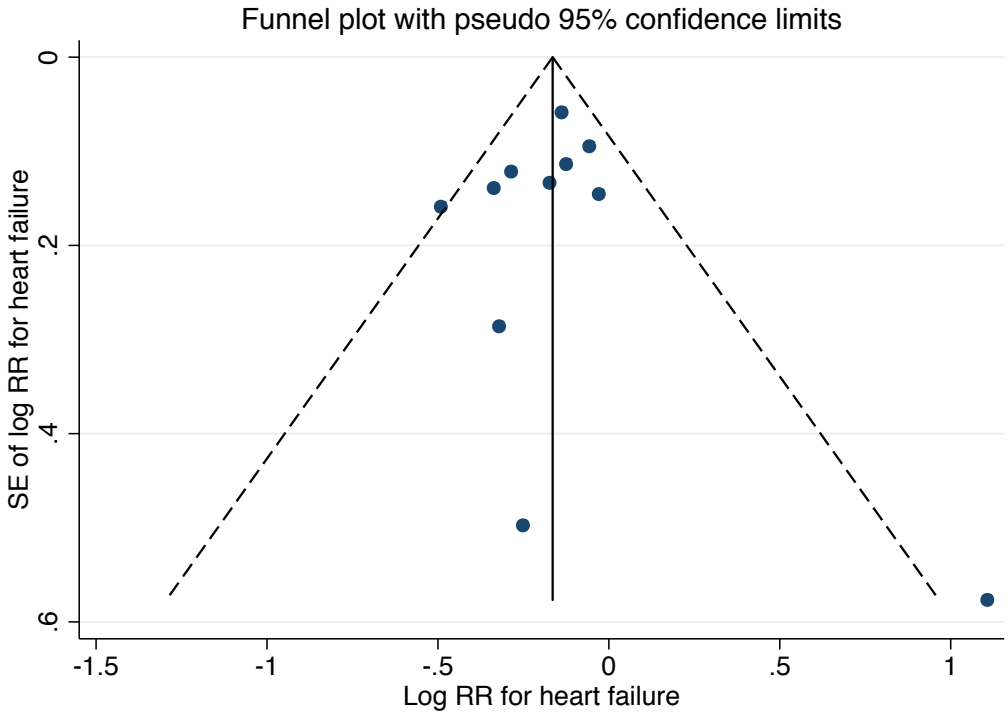
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.599

eFigure 22 – Funnel plot for stroke



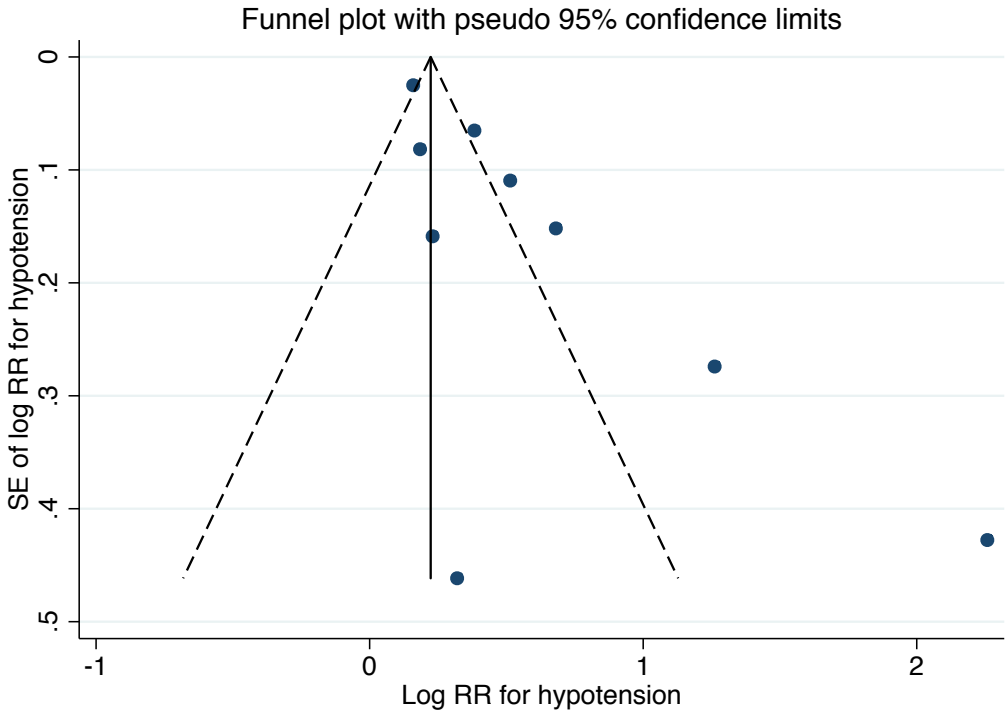
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.267

eFigure 23 – Funnel plot for heart failure



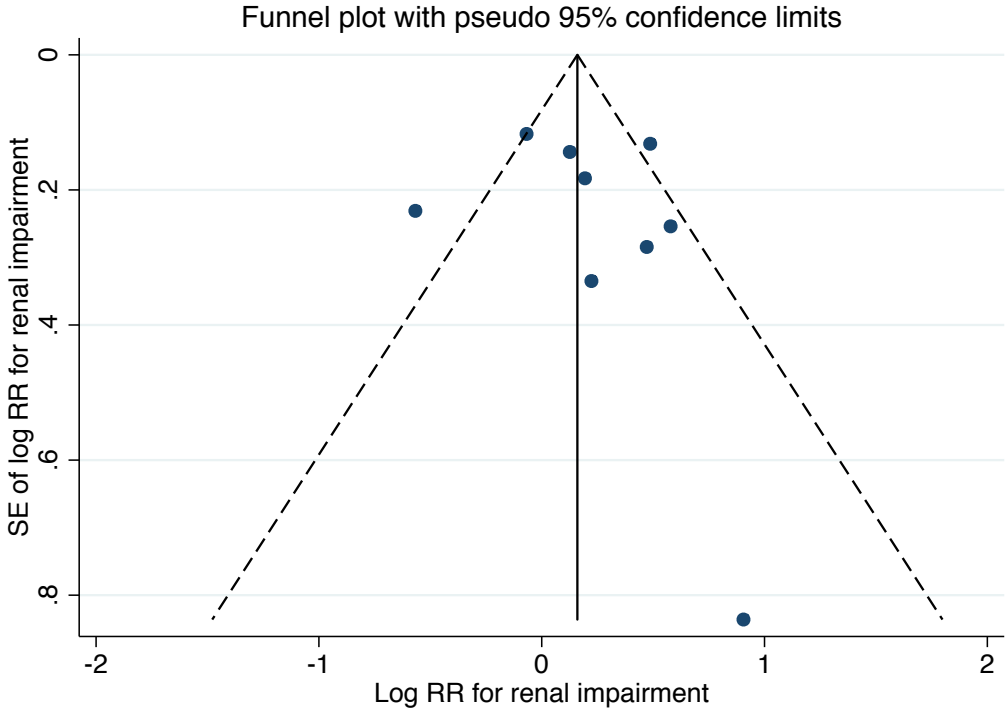
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.854

eFigure 24 – Funnel plot for hypotension-related adverse events



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.060

eFigure 25 – Funnel plot for renal impairment



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.655

eTable 1 – Studies excluded due to high risk of bias or missing data

Study ID	Reason for exclusion
DIRECT Prevent 1[1] DIRECT Protect 1[1] DIRECT Protect 2 [1,2]	Cardiovascular events were evaluated as adverse events, and therefore not blinded. Also, cardiovascular events were not followed-up in people who discontinued treatment, meaning that > 700 patients were lost to follow-up regarding these events. Based on the above, we judge the DIRECT trials to be at high risk of both detection bias and attrition bias.
EUCLID [3]	No outcome data
HDFP [4]	Patients in the intervention group and patients in the control group were treated at different clinics. We therefore judge this trial to be at high risk of performance bias.
Hunan study [5]	Original publication could not be retrieved. Data from previous meta-analyses were of uncertain quality. For example number of strokes differed by tenfold in the analyses by Ettehad et al. and Law et al. Risk of bias assessment could not be made.
INTACT [6]	No blood pressure difference between groups.
MDRD [7]	No outcome data.
NICOLE [8]	No blood pressure data.
PATS [9]	30 % of patients were lost to follow-up. This was about five times the number of events, which means this trial is at high risk of attrition bias.
STONE [10]	Randomisation likely to have failed based on large difference in number of participants in each treatment arm. We judged this trial to be at high risk of selection bias.
Suzuki -08 [11]	All patients received hemodialysis and there was no difference in blood pressure between treatment groups. Although hemodialysis was not a pre-specified exclusion criteria, it alters physiology, affecting blood pressure and drug pharmacokinetics in such a way that the results in these patients are not applicable to the general population.
Syst-China [12]	Treatment allocation was not random. Therefore this trial is at high risk of selection bias and does not fulfil the inclusion criteria of this systematic review.
USPHS [13]	> 30 % of patients dropped out, not specified how many were lost to follow-up respectively followed for outcomes. Vital status not known for 26 patients, compared to 6 deaths. This suggests high risk of attrition bias. Furthermore, treatment groups differed by 2 mm Hg in systolic blood pressure at baseline, and 60 % vs 40 % on prior antihypertensive therapy.

Note: Several of the studies presented above were outside the eligible blood pressure range. They are presented here because exclusions based of risk of bias were done before selection on blood pressure data.

eTable 2 - Absolute risk of MACE in primary preventive trials

Study ID	Pts (n)	MACE (n)	Follow-up (y)	10-year MACE-rate (%) *
ACTIVE I	9016	1926	4.1	52
ALTITUDE	8561	1129	2.7	49
BCAPS	793	18	3.0	7.6
DREAM	5269	56	3.0	3.5
HOPE-3	12705	539	5.6	7.6
Lewis -93	409	-	3.0	-
NAVIGATOR	9306	752	6.5	12
PHARAO	1008	13	3.0	4.3
PREVEND-IT	864	42	3.8	13
ROADMAP	4447	-	3.2	-
Ravid -98	194	-	6.0	-
VA-NEPHRON	1448	270	2.2	85

Pts = participants. MACE = major cardiovascular events.

* 10-year MACE-rate was calculated as (MACE/Pts)x(10/duration).

eTable 3 - Risk of bias table

Study acronym	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
ACTION [14]	Low	Low	Low	Unclear	Low	Low	Low
ACTIVE I [15]	Low	Low	Low	Low	Low	Low	Low
ALTITUDE [16]	Low	Low	Low	Low	Unclear	Low	High
BCAPS [17]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
DREAM [18]	Low	Low	Low	Low	Unclear	Low	Low
EUROPA [19]	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
HOPE [20]	Low	Low	Low	Low	Low	Low	High
HOPE-3 [21]	Low	Low	Unclear	Low	Low	Low	Low
Lewis -93 [22]	Low	Low	Low	Low	Low	High	Low
NAVIGATOR [23]	Low	Low	Low	Low	Unclear	Low	Low
PART-2 [24]	Low	Low	Low	Unclear	Low	Low	Low
PEACE [25]	Low	Low	Low	Unclear	Low	Low	Low
PHARAO [26]	Low	Low	Unclear	Low	Low	Low	Low
PREVEND-IT [27]	Low	Low	Low	Low	Unclear	Low	Low
Ravid -98 [28]	Low	Low	Low	Low	Unclear	Low	Low
ROADMAP [29]	Low	Low	Low	Unclear	Low	Low	Low
SCAT [30]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
VA-NEPHRON [31]	Low	Low	Low	Unclear	Unclear	Low	Low

eTable 4 - Hypotension-related adverse events

Study ID	Pts (n)	Events (n)	RR for hypotension
NAVIGATOR	8 401	3 644	1.17
ACTION	7 305	558	1.20
HOPE	9 297	158	1.26
VA NEPHRON	1 409	19	1.38
ALTITUDE	8 339	876	1.47
HOPE-3	12 592	347	1.67
ACTIVE I	8 976	191	1.98
EUROPA	12 215	77	3.53
ROADMAP	4 341	64	9.56

Note: the apparent asymmetry in the funnel plots is not primarily due to smaller studies having extreme results; rather studies with few events show larger relative risks. This should be interpreted cautiously, but might represent different thresholds for reporting adverse events in different trials, with larger relative risks for more severe events.

eResults - Risk of bias assessment and description

Risk of bias was judged as low when we found a clear description that fulfilled the criteria for low risk of bias according to Cochrane Collaborations risk of bias assessment tool. Risk of bias was judged as unclear if we could not find an adequate description, or if the described methods did not fulfil the criteria for either low or high risk of bias. High risk of bias was assigned when we found a description of a study characteristic of methodological feature known to be associated with biased effect estimates.

All included studies were described as randomized double-blind placebo-controlled trials. Studies judged be at unclear risk of bias for the first three domains generally provided no further description of how randomization and/or blinding was achieved, yet we have no reason to believe it failed. Trials judged to be at unclear risk of bias in the forth domain generally described that outcomes were assessed by a separate committee, but did not explicitly describe this committee as blinded.

Several trials were judged to be at unclear risk of bias for incomplete outcome data. We used this label when attrition was small and asymmetric (ALTITUDE), or when loss to follow-up-rates were higher than event-rates (others). None of the included trials had large and asymmetric loss to follow-up.

Lewis -93 reported myocardial infarction, stroke, and heart failure for both groups combined, and is therefore judged to be at high risk of bias for these outcomes. This is not likely to affect overall results, however, because Lewis -93 was a small study with very few events compared to overall analyses.

We assessed early termination, changes in protocol and sponsor involvement as other potential sources of bias. In EUROPA, the definition of the primary outcome changed during follow-up. Although this might affect the interpretation of the study findings, outcomes used in our analyses where based on pre-defined criteria and not on whether they were primary or secondary in individual studies. Thus it should have little impact on our analyses.

ALTITUDE and HOPE were stopped pre-term due to interim findings. ALTITUDE was stopped due to an increased risk of stroke in the intervention group, whereas HOPE was stopped due to decreased risk of major cardiovascular events in the intervention group. To test the impact of these trials on overall results, we performed ad-hoc sensitivity analyses where they were excluded. Exclusion of ALTITUDE from the primary preventive stroke analysis moved the estimate slightly more towards benefit (relative risk 0.83, 95 % confidence interval 0.68-1.01, compared to 0.89, 0.73-1.09 when ALTITUDE was included). Exclusion of HOPE from the MACE analysis for CAD trials moved the estimate slightly towards neutrality (0.88, 0.78-0.99, compared to 0.85, 0.77-0.94 when HOPE was included).

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8 + Suppl.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8 + Suppl.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8 + Suppl.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Suppl.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 1 & 2 Suppl.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12 Fig. 1 & 2 Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13 + Suppl.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13 + Suppl.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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BMJ Open

Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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2 figures

2 tables

Key words: Hypertension; Antihypertensive agent; Systolic blood pressure; Systematic Review; Meta-analysis

Abstract

Objectives

To assess the effect of antihypertensive treatment in the 130-140 mm Hg systolic blood pressure range.

Design

Systematic review and meta-analysis.

Information sources

PubMed, CDSR and DARE were searched for systematic reviews, which were manually browsed for clinical trials. PubMed and CENTRAL were searched for trials directly in February 2018.

Eligibility criteria

Randomized double-blind trials with ≥ 1000 patient-years of follow-up, comparing any antihypertensive agent against placebo..

Data extraction and risk of bias

Two reviewers extracted study-level data, and assessed risk of bias using Cochrane Collaborations risk of bias assessment tool, independently.

Main outcomes and measures

Primary outcomes were all-cause mortality, major cardiovascular events and discontinuation due to adverse events. Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related adverse events and renal impairment.

Results

Eighteen trials, including 92 567 participants (34 % women, mean age 63 years), fulfilled the inclusion criteria. Primary preventive antihypertensive treatment was associated with a neutral effect on all-cause mortality (relative risk 1.00, 95 % confidence interval 0.95 to 1.06) and major cardiovascular events (1.01, 0.96 to 1.05), but an increased risk of discontinuation due to adverse events (1.23, 1.03 to 1.47). None of the secondary efficacy outcomes were significantly reduced, but the risk of hypotension-related adverse events increased with treatment (1.71, 1.32 to 2.22). In coronary artery disease secondary prevention, antihypertensive treatment was associated with reduced risk of all-cause mortality (0.91, 0.83 to 0.99) and major cardiovascular events (0.85, 0.77 to 0.94), but doubled the risk of adverse events leading to discontinuation (2.05, 1.62 to 2.61).

Conclusion

Primary preventive blood pressure lowering in the 130 to 140 mm Hg systolic blood pressure range adds no cardiovascular benefit, but increases the risk of adverse events. In secondary prevention benefits should be weighed against harms.

Registration

Registered in PROSPERO, registration number CRD42018088642.

Article Summary

Strengths and limitations of this study

- Meta-analysis restricted to randomized double-blind placebo-controlled trials, thereby minimizing the risk of performance bias
- Adverse events included as co-primary outcome, putting emphasis on both benefits and harms
- Separate analyses for primary and secondary preventive trials, reducing the risk of confounding from coronary artery disease and increasing the usefulness of the results in different clinical contexts
- Main limitation is the use of study-level data, with the potential for ecological bias.

Introduction

For decades, hypertension has been defined as a blood pressure (BP) ≥ 140/90 mm Hg.[1] The definition has been uniform across the world, and for most patients the recommended treatment goal has been < 140/90 mm Hg.[2-4] In 2017, the American Collage of Cardiology (ACC) and the American Heart Association (AHA) updated the U.S. guidelines, changing the definition of hypertension to ≥ 130/80 mm Hg.[5] For secondary preventive patients, and for primary preventive patients with a 10-year cardiovascular risk ≥ 10 per cent, the treatment goal is now < 130/80 mm Hg. Recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) followed, retaining the old definition of hypertension, but lowering the treatment goal to 120-130/70-80 mm Hg for most patients [6]

The revision of both sets of guidelines were heavily influenced by the Systolic Blood Pressure Intervention Trial (SPRINT).[7] SPRINT randomized > 9 000 high-risk patients (without previous stroke or diabetes) to a systolic blood pressure (SBP) target < 120 mm Hg compared to < 140 mm Hg, and was stopped preterm due to lower risk of death and cardiovascular disease in the intensive treatment group.[7] In addition to SPRINT, the ACC/AHA performed a systematic review and meta-analysis including only non-blinded randomized trials comparing different treatment goals.[8]

Blinding of participants and study personnel is desirable to minimize the risk of performance bias.[9] In non-blinded studies, such as SPRINT and those included in the ACC/AHA systematic review, participants may be handled differently depending on treatment group, thereby cofounding the assessment of the intervention. Meta-epidemiological studies have found that trials with unclear or incomplete blinding

produce more favourable results compared to trials that are double-blind.[10] Additionally, in the clinic, we know the patients' blood pressure, but not what blood pressure he or she will have after adding an additional drug. Placebo-controlled trials mimic the clinical situation where the question is – should we add another drug or not?

This systematic review and meta-analysis aims to evaluate the benefits and harms associated with antihypertensive treatment in randomized double-blind placebo-controlled trials with mean SBP 130-140 mm Hg at randomization. Such an approach eliminates the risk of performance bias, yet produces treatment effect estimates reasonably specific for the SBP interval for which the new recommendations differ from previous ones. Because the ACC/AHA systematic review was restricted to non-blinded target trials and this review is restricted to placebo-controlled trials of different agents, our analyses serves as validation of the ACC/AHA systematic review findings in a different population with theoretically more robust methods.

Methods

We performed a systematic review and meta-analysis guided by the recommendations from the Cochrane Collaboration.[9] A protocol was registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42018088642. Reporting follows the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Studies were eligible if they were randomized double-blind placebo-controlled trials with ≥ 1000 patient-years of follow-up; assessing the effect of any antihypertensive

agent against placebo, with mean baseline SBP ≥ 130 mm Hg and < 140 mm Hg. The 1000 patient-year cut-off was chosen to reduce the risk of small-study bias. Target-driven trials were excluded due to reasons described above, and trials comparing different antihypertensive agents against each other were excluded because they risk assessing blood pressure-independent effects of agents. [9,10] We also excluded trials in patients with acute myocardial infarction or heart failure/left ventricular dysfunction because several antihypertensive agents are thought to affect on clinical outcomes through blood pressure-independent mechanisms, like reduced preload, reduced afterload and sympathetic inhibition, in these settings.[12,13]

We used one of our recent, more comprehensive systematic reviews, assessing treatment effect of antihypertensive treatment across blood pressure levels in a wide range of patient categories, for study selection.[14] Search strategies for the previous review are presented in the online supplement (eMethods). In addition, we searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from the date of the previous search until February 2018, using search terms ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke). Titles were screened by M.B. and apparently irrelevant publications were removed. Two authors judged abstracts separately, after which final decision on eligibility was reached through discussion (eFigure 1).

Data were extracted from the included studies into specially designed Excel sheets by two authors separately. When extracted data differed between authors, we revisited original publications. Descriptive data were collected on study level, whereas blood pressure data and outcome data were collected for each treatment group individually.

All trials were judged for risk of bias by two authors separately, using Cochrane Collaboration´s Risk of Bias assessment tool.[15] The risk of bias tool covers six specific domains related to randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, attrition and outcome reporting. Also, we assessed sponsor involvement, protocol changes and premature study discontinuation as other potential sources of bias. Trials judged to be at high risk of selection bias, performance bias, detection bias or attrition bias (first five domains), were excluded from all analyses (eTable 1). Risk of bias for selective reporting should be considered interpreting the overall analyses for each outcome rather than individual trials, because lack of data, rather than biased data, may produce biased overall results.[9, 15]

Primary outcomes were all-cause mortality, MACE (defined as cardiovascular death, myocardial infarction and stroke if not specified otherwise), and discontinuation due to adverse events (AEs). Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related AEs, and discontinuation due to renal impairment/acute kidney injury.

Results were analyzed according to the intention-to-treat principle, in the sense that participants were analyzed in their assigned treatment group. When study participants were lost to follow-up, relative risks (RR) were calculated using complete cases in the denominator, according to the recommendations from the Cochrane Collaboration.[9] In two sets of sensitivity analyses, we calculated RRs using the observed number of events in the numerator and the total number of randomized participants in the denominator (assuming that all participants lost to follow-up were event free), and the observed number of events plus number of participants lost to follow-up in the numerator and the

total number of randomized participants in the denominator (assuming that all participants lost to follow-up had experienced an event). RRs were not standardized for BP differences in trials, because such standardization is associated with increased heterogeneity, unbalanced study weights, and biased overall results.[16]

Relative risks from individual trials were pooled using DerSimonian-Laird random-effects meta-analyses. We separated primary preventive studies from studies in people with established coronary artery disease (CAD), because these represent clinically different populations, and because we have previously observed potentially different treatment effects in these groups.[14] Trials with mixed populations were classified as CAD trials if ≥ 50 % of participants had previous CAD. Treatment effect interaction between primary preventive studies and CAD studies was assessed using random-effects metaregression. Pre-specified sensitivity analyses, excluding trials in people with diabetes, trials of dual renin-angiotensin-aldosterone system (RAAS) inhibition, trials not reaching < 130 mm Hg in the intervention group, trials of previously treated/hypertensive patients, and trials of treatment naïve patients, were performed to test the impact of different patient/trial characteristics on overall results for primary outcomes. We explored potential effect modification by diabetes and absolute cardiovascular risk as continuous explanatory variables using random-effects metaregression. Lastly, we performed ad-hoc subgroup analyses, stratifying primary preventive trials by 10-year MACE event-rate above versus below 10 %, to approximate the cut-off used in the 2017 ACC/AHA guidelines.[5]

Between-study heterogeneity in meta-analyses was assessed calculating I-squared, which represents the percentage of variance between studies that cannot be explained

by chance alone. When statistical heterogeneity was present we sought for corresponding clinical heterogeneity. If statistically deviating studies differed with respect to clinical characteristics, they were excluded in sensitivity analyses. Small-study effects were assessed through funnel plots for all primary and secondary outcomes, using Harbord´s test for asymmetry.[17] All analyses were performed using STATA v12.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advice on interpretation or writing up of results. Since we used only aggregated data from previous trials, we are unable to disseminate the results of the research to study participants directly.

Results

Eighteen trials[18-35], including 92 567 participants (34 % women; mean age 63 years), fulfilled the inclusion criteria (table 1). During an average of 4.5 years under randomized double-blind treatment, 2 042 participants were lost to follow-up (2.2 %), resulting in 90 525 complete cases and 407 000 patient-years of follow-up. Twelve trials[19-22,25-27,30-33,35], including 54 020 participants, were classified as primary preventive. Mean baseline SBP in primary preventive trials was 138 mm Hg, mean follow-up SBP was 132 mm Hg respectively 135 mm Hg with active treatment versus placebo, with a weighted mean difference between groups of 3.4 mm Hg. Six trials[18,23,24,28,29,34], including 38 547 participants, were classified as CAD trials; mean

baseline SBP was 137 mm Hg, mean follow-up SBP was 130 mm Hg in the active treatment group, 134 mm Hg in the placebo group, with 4.2 mm Hg difference between groups.

In primary prevention (figure 1), treatment was not associated with any effect on all-cause mortality (relative risk 1.00, 95 % confidence interval 0.95 to 1.06) or MACE (1.01, 0.96 to 1.05), but an increased risk of AEs leading to discontinuation (1.23, 1.03 to 1.47). In CAD trials (figure 2), treatment reduced the risk of all-cause mortality by 9 % (0.91, 0.83 to 0.99), and the risk of MACE by 15 % (0.85, 0.77 to 0.94), but doubled the risk of AEs leading to discontinuation (2.05, 1.62 to 2.61). Heterogeneity was low in mortality and MACE analyses for primary prevention, moderate to high in CAD trials, and very high for AEs in both cohorts. The difference between primary preventive trials and CAD trials was significant for MACE (p=0.019) and borderline for all-cause mortality and AEs (p=0.051 respectively 0.070).

None of the secondary efficacy outcomes were affected by primary preventive treatment (table 2; online supplement eFigure 2-7). Hypotension-related AEs increased by 71 % (1.71, 1.32 to 2.22) whereas discontinuation due to renal impairment showed a non-significant tendency towards harm (1.20, 0.93 to 1.55). Of note, heterogeneity was high in the renal impairment analysis, mostly due to one study in patients with type 1-diabetes and macroalbuminuria.[26] When this study was removed in a sensitivity analysis, heterogeneity decreased and the observed risk increase became nominally significant (1.30, 1.06 to 1.58).

In CAD trials (table 2; online supplement eFigure 2-7), treatment reduced the risk of myocardial infarction (0.83, 0.72 to 0.97), stroke (0.79, 0.66 to 0.94), heart failure (0.76, 0.67 to 0.86), and cardiovascular death (0.86, 0.74 to 1.00, p=0.047). Differences between primary prevention and CAD trials were significant or borderline significant for all efficacy outcomes except stroke (eFigure 2-7). The relative risk of adverse events was similar as in primary preventive studies, although estimates were less precise and reporting was poor (only one trial reported renal impairment).

Sensitivity analyses, testing the impact of different trial characteristics, shifted effect estimates slightly (eFigure 8-12), but not enough to affect the interpretation of our main findings. Metaregression analyses, exploring potential effect modification by observed cardiovascular risk and diabetes mellitus were non-significant. Both sensitivity analyses and metaregression analyses should be interpreted carefully due to small number of trials. Of note, the absolute 10-years risk of MACE was well above the 10% threshold for recommending treatment in the ACC/AHA guidelines, with an average risk across studies of 26 % (eTable 2); subgroup analyses of primary preventive trials stratified by 10-year cardiovascular event-rate found no interaction between risk of MACE and treatment effect (eFigure 13).

Risk of bias was generally judged as low for individual trials (eTable 3 & eResults). We required studies to be described as randomized double-blind placebo-controlled trials to be eligible. Loss to follow-up was limited, and sensitivity analyses imputing all participants lost to follow-up as either having an event or being event-free did not alter effect estimates (eFigure 14-15). Three trials were judged to be at high risk of bias for individual domains.[20,24,26] We performed sensitivity analyses, testing the impact of these

trials on our primary outcomes (eFigure 16). This had marginal effects on relative risks and confidence intervals, but no effect on nominal significance for any analysis.

Funnel plots showed no signs of asymmetry (eFigure 17-25), although such analyses should be interpreted carefully due to the small number of trials. The possible exception was hypotension-related adverse events where interaction was borderline significant despite low statistical power (p=0.06). When we explored this further, we found that treatment effect correlated with number of events but not study size (eTable 4). The frequency of hypotension-related AEs varied by a factor of 50 between trials, presumably representing different thresholds for reporting. Thus, the observed association between number of adverse events and the relative risk of adverse events might represent a stronger association between treatment and severe events compared to less severe events.

Discussion

This systematic review and meta-analysis evaluates if antihypertensive treatment in the 130-140 mm Hg SBP interval is supported by findings from randomized double-blind placebo-controlled trials. This does not seem to be the case in primary prevention, with no treatment effect on all-cause mortality or MACE, but an increased risk of AEs leading to discontinuation. In people with previous CAD, treatment might be beneficial, though these findings should be interpreted more cautiously due to statistical heterogeneity and wider confidence intervals. While the type of trials included here do not assess SBP targets by design, they correspond to the clinical situation of adding an extra pill to

patients with a SBP between 130 and 140 mm Hg. Overall, the results presented here do not support such treatment, except for in patients with established CAD.

This paper has several important limitations that need to be addressed. Firstly, we only had access to aggregated data, making analyses susceptible to ecological bias. Studies were included based on average SBP levels, meaning that individual participants with an SBP > 140 mm Hg or < 130 mm Hg were included in the analyses because the average SBP in their trials were within the accepted range. Similarly, individual participants with an SBP within our accepted range were missed because they were included in trials with an average SBP outside our accepted range. Notably, this problem is not unique to this review, but applies to most meta-analyses in the field, including those comparing different blood pressure targets cited by guidelines. [8,36,37] Overcoming this would require individual-patient data, unfortunately not available to date. Secondly, the aggregated nature of our data also affects categorization of trials as primary or secondary preventive. In trials categorized as primary preventive, 17 % of participants had CAD, whereas in secondary preventive trials the corresponding number was 95 %. This represents reasonable separation between groups, although this aspect could also be explored further in individual-patient data meta-analyses. Thirdly, additional possible effect modifiers like age, sex, and other comorbidities would also require individual-patient data and were therefore not assessed. Fourthly, SBP was only moderately reduced in the trials included in our analyses; less so compared to previous meta-analyses including target-driven trials. Although a less pronounced effect on clinical outcomes would be expected, the observed SBP difference of 3.4 mm Hg during > 200 000 person-years of follow-up should have resulted in at least a tendency towards primary preventive benefit if such were present. Instead confidence intervals were fairly

narrow around the null effect. Fifthly, all but two of the included trials assessed the effect of renin-angiotensin-aldosterone system (RAAS) inhibitors. Whereas the generalizability of our findings to other drugs therefore could be questioned, previous meta-analyses have found no clinically meaningful difference between RAAS inhibitors and other first-line agents for hypertension control.

The arguments for lowering SBP treatment goals differ slightly between the ACC/AHA guidelines compared to the ESH/ESC guidelines.[5,6] Common to both sets of guidelines is that they put emphasis on the results of systematic reviews and meta-analysis. Whereas the ACC/AHA performed their own systematic review of trials comparing different targets,[8] the ESH/ESC refers mainly to two previously published papers combining results from target-trials and placebo-controlled trials.[36,37]

The main strength of this review, compared to the systematic reviews underlying the ACC/AHA and the ESH/ESC guidelines, is that it is limited to randomized double-blind placebo-controlled trials, protecting it against performance bias. Although the magnitude of this potential problem is unknown, target-driven trials may be susceptible to performance bias due to their non-blinded nature.[9] Possible indicators of such bias might be 20-30 % more unscheduled visits in the intensive treatment group, and a large non-cardiovascular component of the all-cause mortality reduction, seen in SPRINT.[7] Meta-analyses restricted to target-trials, such as the one by the ACC/AHA[8], may be especially susceptible to these kinds of biases, whereas the risk is probably lower in meta-analyses combing target-trials and placebo-controlled trials, such as those underlying the ESH/ESC recommendations.[36,37] Notwithstanding, the different findings in our analysis compared to the ACC/AHA analysis should raise the question if

performance bias does play a role in target-trials of antihypertensive treatment, exaggerating treatment effect estimates.

Another important difference between this analysis and the ones underlying the ACC/AHA and ESH/ESC guidelines is that we analyze primary preventive studies and secondary preventive studies separately. This is important because the evidence for BP lowering in the 130-140 mm Hg interval comes to a large extent from trials in people with established coronary artery disease (CAD). Before primary and secondary preventive trials are combined one has to ask if it is reasonable to extrapolate findings from CAD patients to healthy individuals. To answer this, it is important to consider possible mechanistic differences in these populations. In primary prevention, development of atherosclerosis is a sine qua non for succeeding cardiovascular events, and hence the effect of BP lowering treatment on the early stages of atherosclerosis becomes most important. In people with established CAD, on the other hand, angina and heart failure symptoms are closely related to myocardial oxygen balance, depending to a large extent on cardiac afterload which is proportional to systolic blood pressure.[38] Also, systolic blood pressure has been associated with changes in atheroma size, indicating that higher blood pressure may increase the risk of plaque rupture.[39] Therefore, it is not beyond reasonable doubt that BP lowering might work through different mechanisms depending on CAD status; in this situation, lumping trials with and without CAD patients should be avoided. The analyses presented here provide statistical support to the pathophysiologically based decision to separate patient categories. Indeed, it shows that the observed benefit in previous analyses depends on inclusion of secondary preventive studies.

Lastly, the systematic reviews referred to as supportive of lower treatment targets in the ESH/ESC guidelines used meta-analyses standardized to systolic BP reductions of 10 mm Hg.[36,37] This might seem reasonable at first, but affects the results in ways that might not be clear to most readers.[16] Firstly, standardization amplifies treatment effects by about 50 %, because SBP reduction in the included trials was on average 6-8 mm Hg whereas results are standardized to 10 mm Hg. Secondly, standardization assumes that there is a linear association between blood pressure reduction and cardiovascular outcomes, which may not be the case in this blood pressure interval and may also be different for different outcomes. If indeed the association between BP reduction and cardiovascular event reduction were linear, one would expect decreased heterogeneity with standardization. Our previous results indicate that standardization increases heterogeneity and makes analyses highly sensitive to choice of statistical methods.[16] This is probably due to amplification of differences not related to BP lowering, paradoxically making standardized results less blood pressure-dependent. Thirdly, standardization of standard errors, which was applied in one of the referred meta-analyses, disrupts the association between number of events within trials and weight given to trials in meta-analyses.[16,36] For example, the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial, were given 7.3 % weight the all-cause mortality analysis, despite contributing with less than 0.3 % of participants.[36] Simply put, standardization makes results less representative of the underlying data.

Although arguments can be made for including target-trials, lumping different populations and using standardization, all these approaches build on assumptions that the current analysis does not. If treatment benefit hinges on these assumptions, results are simply not robust enough to change guidelines for hundreds of millions of people

worldwide. Meta-analyses using non-standardized methods have consistently found that the effects of antihypertensive treatment are attenuated at lower BP levels.[14,40-42] In a recent paper, we found 22 % reduced risk of MACE if baseline SBP was > 160 mm Hg, 12 % reduced risk in the 140-159 mm Hg SBP range, whereas in trials with baseline SBP below 140 mm Hg treatment effect was neutral for all efficacy outcomes. These results are well in line with the third Heart Outcomes Prevention Evaluation (HOPE-3) study, where 12 705 participants with average baseline BP 138/82 mm Hg were randomized to candesartan/hydrochlorothiazide combination therapy or matching placebo.[25] In fact, HOPE-3 is the only mega-trial aiming to assess the effect of antihypertensive treatment against double-blind placebo in mostly treatment naïve normotensive primary preventive patients. Neither the primary combined endpoints nor individual cardiovascular outcomes were reduced by treatment. However, there was a significant interaction between baseline SBP and treatment effect on MACE, with treatment benefit in the highest SBP tertile but a tendency towards harm in the lowest SBP tertile.

Treatment decisions should always be based on consideration of both benefit and harm. In situations where interventions are unlikely to be harmful, one may consider treatment despite weak or conflicting evidence. Unfortunately, randomized clinical trials, and systematic reviews of such trials, show incriminating signs of harm for antihypertensive treatment at BP levels now recommended in guidelines. In people with diabetes mellitus, we have previously shown that BP-lowering treatment at SBP levels < 140 mm Hg is associated with 15 % increased risk of cardiovascular death.[40] Further down the ladder of seriousness and irreversibility comes an increased risk of chronic kidney disease,[43] acute kidney injury,[44] as well as hypotension-related adverse events and adverse events leading to treatment discontinuation presented here.

In summary, randomized double-blind placebo-controlled trials do not support primary preventive BP-lowering in the 130-140 mm Hg SBP range. Such treatment does not affect all-cause mortality or incident cardiovascular disease, but increases the risk of adverse events. In people with previous CAD, treatment may reduce the risk of all-cause mortality and MACE, at the cost of more pronounced risk increase for adverse events. In CAD patients, therefore, benefits should be balanced against potential harms for individual patients.

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Table 1. Study characteristics

Acronym (year)	Participants (n, age, sex)	Co-morbidity	Intervention/ Control	Baseline SBP/DBP (mm Hg)	SBP/DBP difference (mm Hg)
ACTION (2004)	7665 63 years 21 % female	100 % CAD 14 % DM	Nifedipine 60 mg vs. placebo	137.5/ 79.8	5.7/ 3.0
ACTIVE I (2011)	9016 70 years 29 % female	36 % CAD 20 % DM 100 % AF	Irbesartan 300 mg vs. placebo	138.3/ 82.4	2.9/ 1.9
ALTITUDE (2012)	8561 64 years 32 % female	26 % CAD 100 % DM 98 % CKD	Aliskiren 300 mg vs. placebo	137.3/ 74.2	1.3/ 0.6
BCAPS (2001)	793 62 years 55 % female	4 % CAD 3 % DM All had carotid plaques	Metoprolol CR/XL 25 mg vs. placebo	138.9/ 84.7	1.3/ -
DREAM (2006)	5269 55 years 59 % female	0 % CAD 0 % DM All had IGT/IFG	Ramipril 15 mg vs. placebo	136/ 83.4	4.3/ 2.7
EUROPA (2003)	12 218 60 years 15 % female	100 % CAD 12 % DM	Perindopril 8 mg vs. placebo	137/ 82	5/ 2
HOPE (2000)	9297 66 years 27 % female	81 % CAD 38 % DM	Ramipril 10 mg vs. placebo	139/ 79	3/ 2*
HOPE-3 (2016)	12 705 66 years 46 % female	0 % CAD 6 % DM	Candesartan/ HCTZ 16/12.5 mg vs. placebo	138.1/ 81.9	6/ 3
Lewis (1993)	409 35 years 47 % female	100 % DM (type 1) All with nephropathy	Captopril 75 mg vs. placebo	138.5/ 85.5	1.5/ 2.5
NAVIGATOR (2010)	9306 64 years 51 % female	24 % CAD 0 % DM 100 % IGT	Valsartan 160 mg vs. placebo	139.7/ 82.6	2.8/ 1.4
PART-2 (2000)	617 61 years 18 % female	68 % CAD (100 % CVD) 9 % DM	Ramipril 5-10 mg vs. placebo	133/ 79	5.5/ 4
PEACE (2004)	8290 64 years 18 % female	100 % CAD 17 % DM	Trandolapril 4 mg vs. placebo	133/ 78	3.0/ 1.2
PHARAO (2008)	1008 62 years 52 % female	6 % CAD 13 % DM	Ramipril 5 mg vs. placebo	134.4/ 83.6	2.8/ 0.9

PREVEND-IT (2004)	864 51 years 35 % female	3 % CAD 3 % DM	Fosinopril 20 mg vs. placebo	130/ 76	3/ 3
Ravid (1998)	194 55 years 51 % female	0 % CAD 100 % DM	Enalapril 10 mg vs. placebo	MAP 97	-/ -
ROADMAP (2011)	4447 58 years 54 % female	25 % CAD 100 % DM	Olmesartan 40 mg vs. placebo	136.5/ 80.5	3.1/ 1.9
SCAT (2000)	460 61 years 11 % female	100 % CAD 11 % DM	Enalapril 10 mg vs. placebo	130/ 77.5	5.2/ 3.3
VA-NEPHRON (2013)	1448 65 years 0.3 % female	23 % CAD 100 % DM with nephro-pathy	Losartan/ lisinopril 100/10-40 mg vs. losartan 100 mg	137.0/ 72.7	1.5/ 1.0

* A sub-study assessing ABPM found larger BP differences between groups during follow-up, indicating potentially underestimated BP differences in the main publication. SBP = systolic blood pressure. DBP = diastolic blood pressure. CAD = coronary artery disease. DM = diabetes mellitus. AF = atrial fibrillation. CKD = chronic kidney disease. IGT = impaired glucose tolerance. IFG = impaired fasting glucose. HCTZ = hydrochlorothiazide. MAP = mean arterial pressure.

Table 2. Secondary outcomes

		Primary prevention trials			Coronary artery disease trials		
		Trials/ participants/ events (n)	RR (95 % CI)	I^2 (%)	Trials/ participants/ events (n)	RR (95 % CI)	I^2 (%)
Efficacy outcomes	Cardiovascular mortality	8 / 49 685 / 2390	1.07 (0.95-1.21)	27.3	5 / 37 589 / 1802	0.86 (0.74-1.00)	55.7
	Myocardial infarction	8 / 46 682 / 1092	1.03 (0.91-1.15)	0.0	5 / 29 893 / 2367	0.83 (0.72-0.97)	60.0
	Stroke	9 / 47 546 / 1536	0.89 (0.73-1.09)	52.9	6 / 38 049 / 943	0.79 (0.66-0.94)	36.6
	Heart failure	6 / 44 881 / 1903	0.90 (0.81-1.00)	17.7	5 / 37 589 / 957	0.76 (0.67-0.86)	0.0
Safety outcomes	Hypotension-related AEs	6 / 44 058 / 5141	1.71 (1.32-2.22)	90.3	3 / 28 817 / 793	1.63 (1.01-2.63)	85.9
	Renal impairment	8 / 49 627 / 992	1.20 (0.93-1.55)	71.6	1 / 12 215 / 36	1.25 (0.65-2.41)	-

RR = relative risk. CI = confidence interval. AEs = adverse events

Figure legends

Figure 1 – Treatment effect on primary outcomes in primary prevention. CI = confidence interval.

Figure 2 – Treatment effect on primary outcomes in coronary artery disease trials. CI = confidence interval.

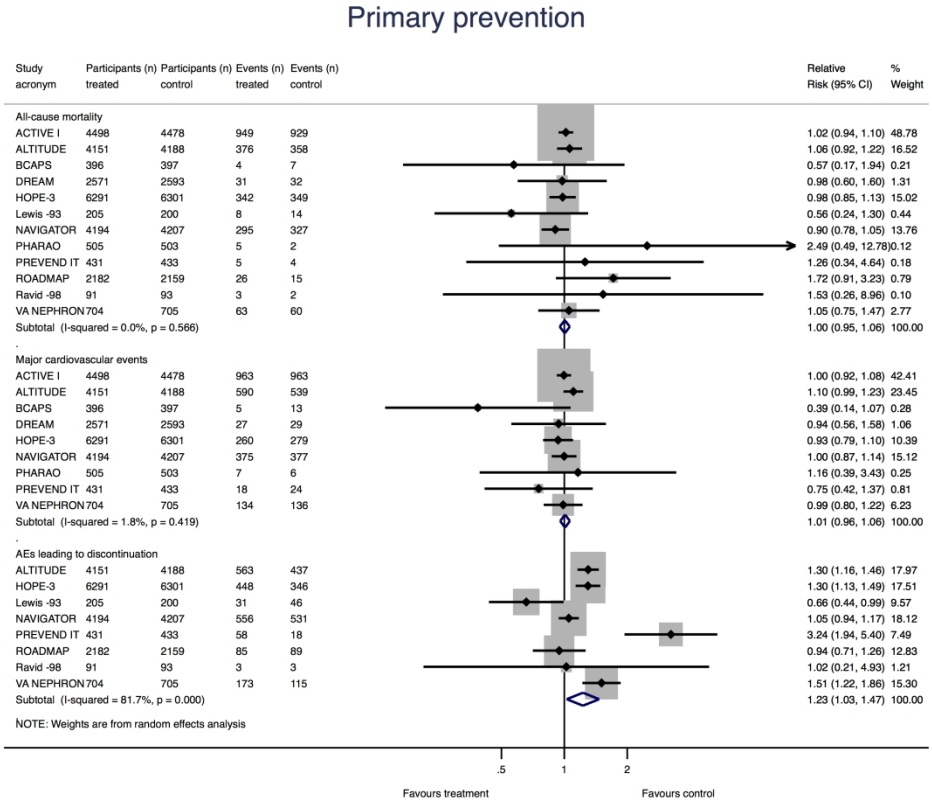

Figure 1 – Treatment effect on primary outcomes in primary prevention. CI = confidence interval.

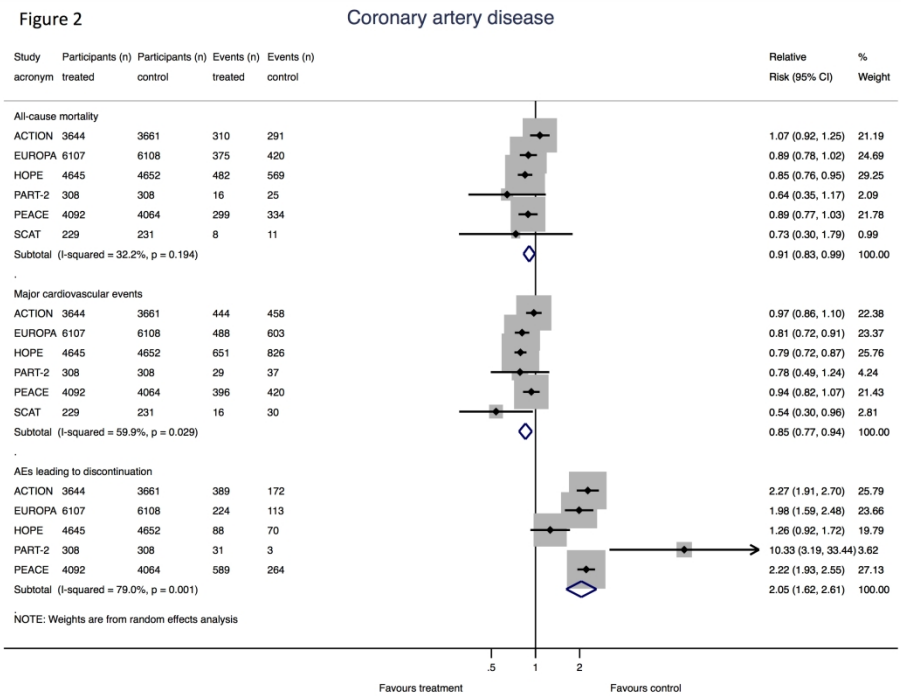

Figure 2 – Treatment effect on primary outcomes in coronary artery disease trials. CI = confidence interval.

ONLINE SUPPLEMENT

Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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eMethods - Search strategy for previous systematic review

The previous systematic review used a two-stage approach. First, we searched for systematic reviews of randomized controlled trials assessing antihypertensive treatment. All trials included in any previous systematic review were judged in full text against our eligibility criteria. We then performed an additional search for randomized controlled trials published after the latest previous search (with a few months overlap to account for time lag in indexing).

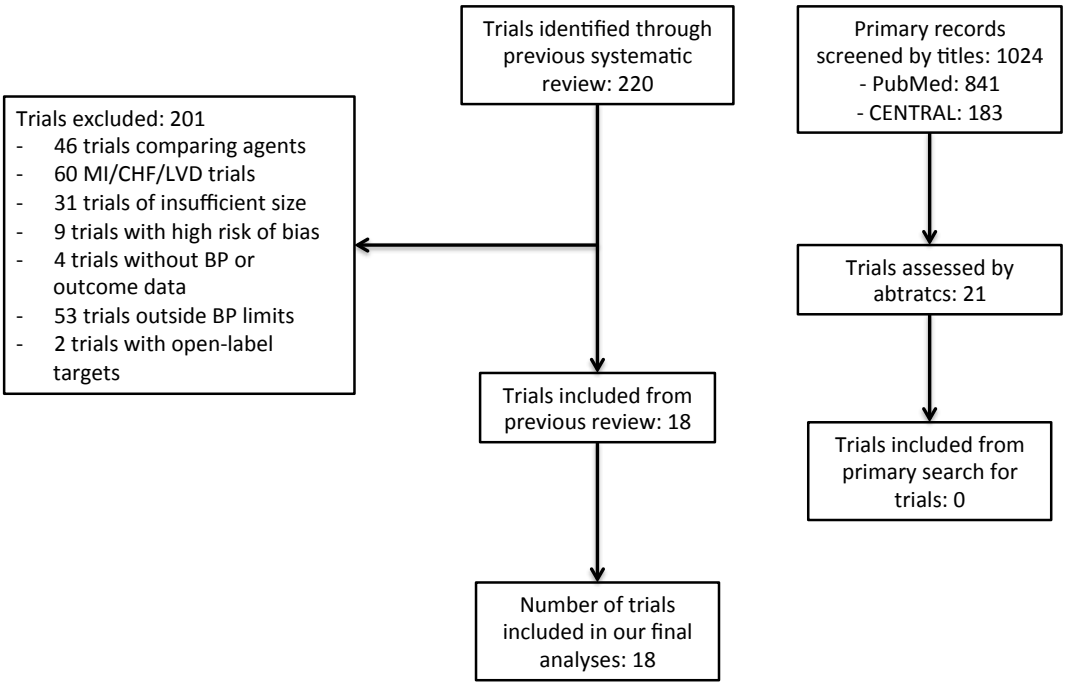
Search strategy systematic reviews
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke) in all databases, adding the filter for meta-analyses in PubMed.

The titles of the retrieved articles were browsed to identify reviews concerning the effect of BP lowering on death, cardiovascular events and renal disease. Reviews concerning treatment of other conditions, effects of specific agents, or the effect of BP lowering on other outcomes, were discarded. All randomized controlled trials included in any of the reviews deemed relevant were retrieved in full text and judged according to the above eligibility criteria.

Search strategy for randomized controlled trials
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke), adding ("2015/11/01"[Date – Publication] : "3000"[Date – Publication]) to the PubMed search and limiting the CENTRAL search to 2015-2017.

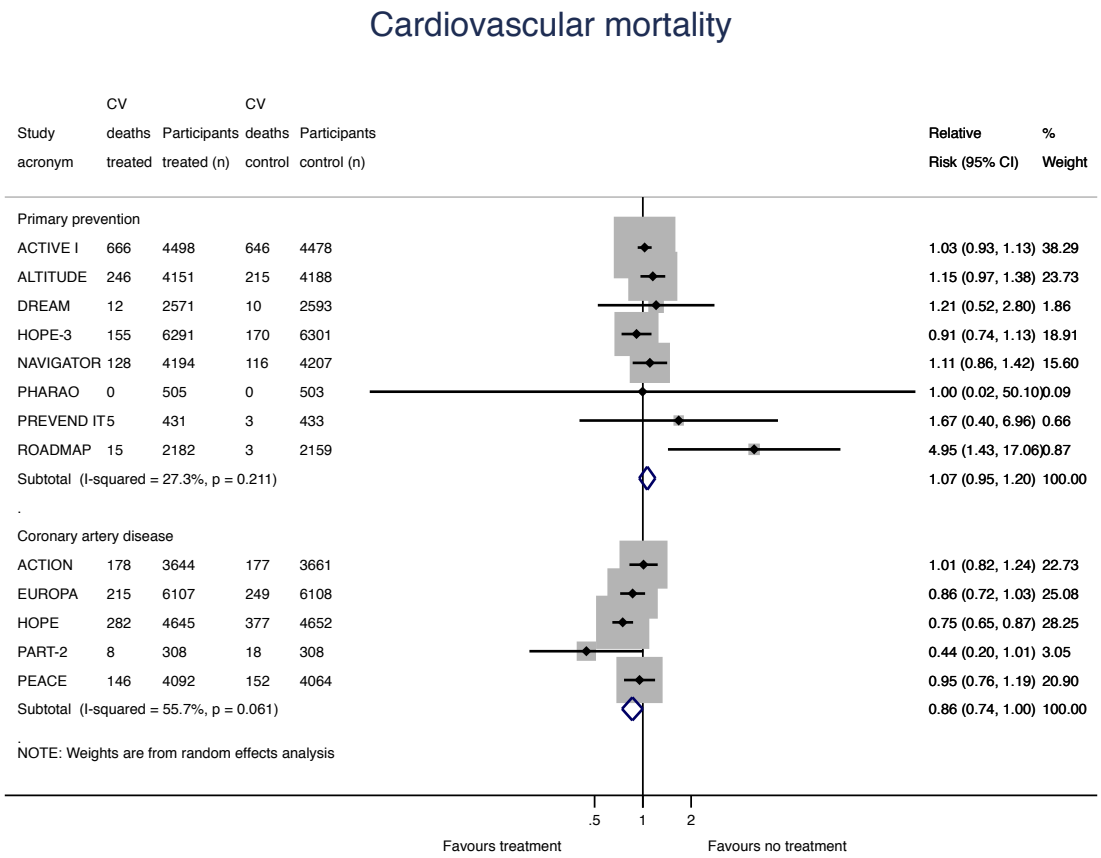
We also performed an alternative PubMed search, using the phrase (("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND ("2015/11/01"[Date - Publication] : "3000"[Date - Publication])) with RCT filter.

eFigure 1 - PRISMA flow chart



CENTRAL = Cochrane Central Register for Controlled Trials. MI = myocardial infarction. CHF = congestive heart failure. LVD = left ventricular dysfunction. BP = blood pressure.

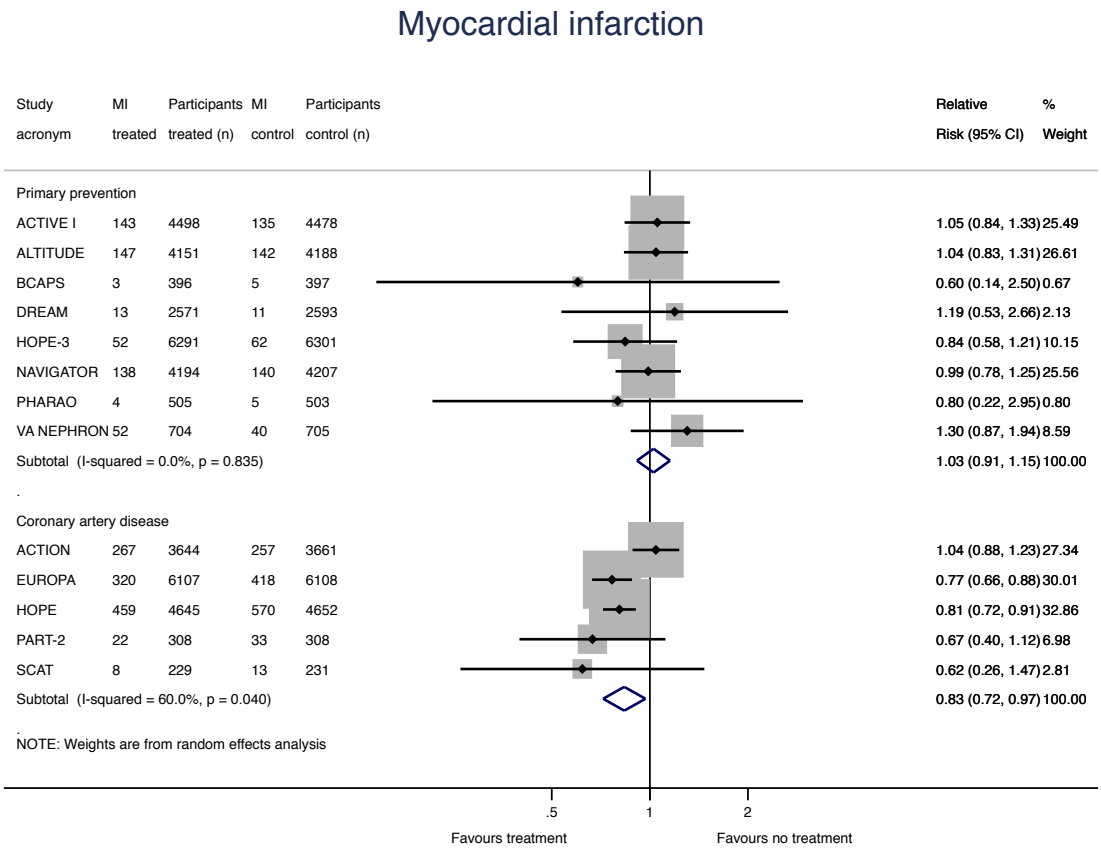
eFigure 2 – Forest plot for cardiovascular mortality



CV = cardiovascular.

Random-effects metaregression for interaction (p=0.047)

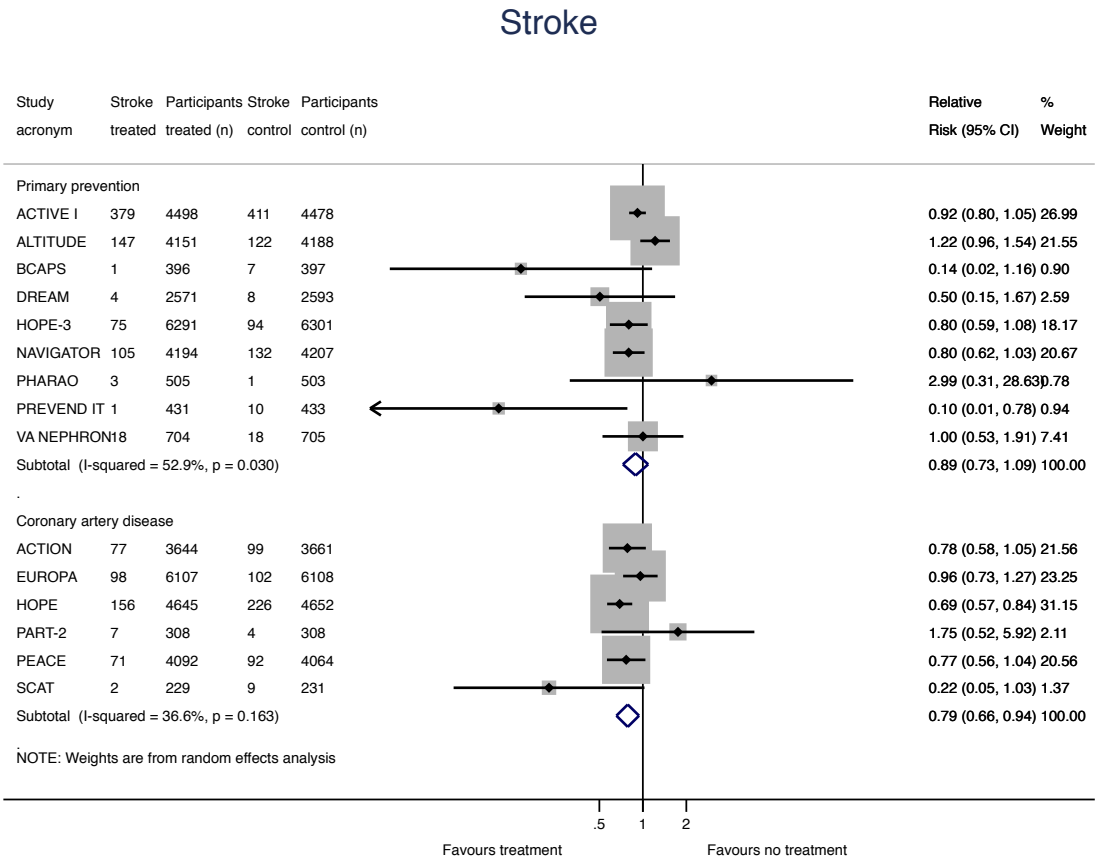
eFigure 3 – forest plot for myocardial infarction



MI = myocardial infarction.

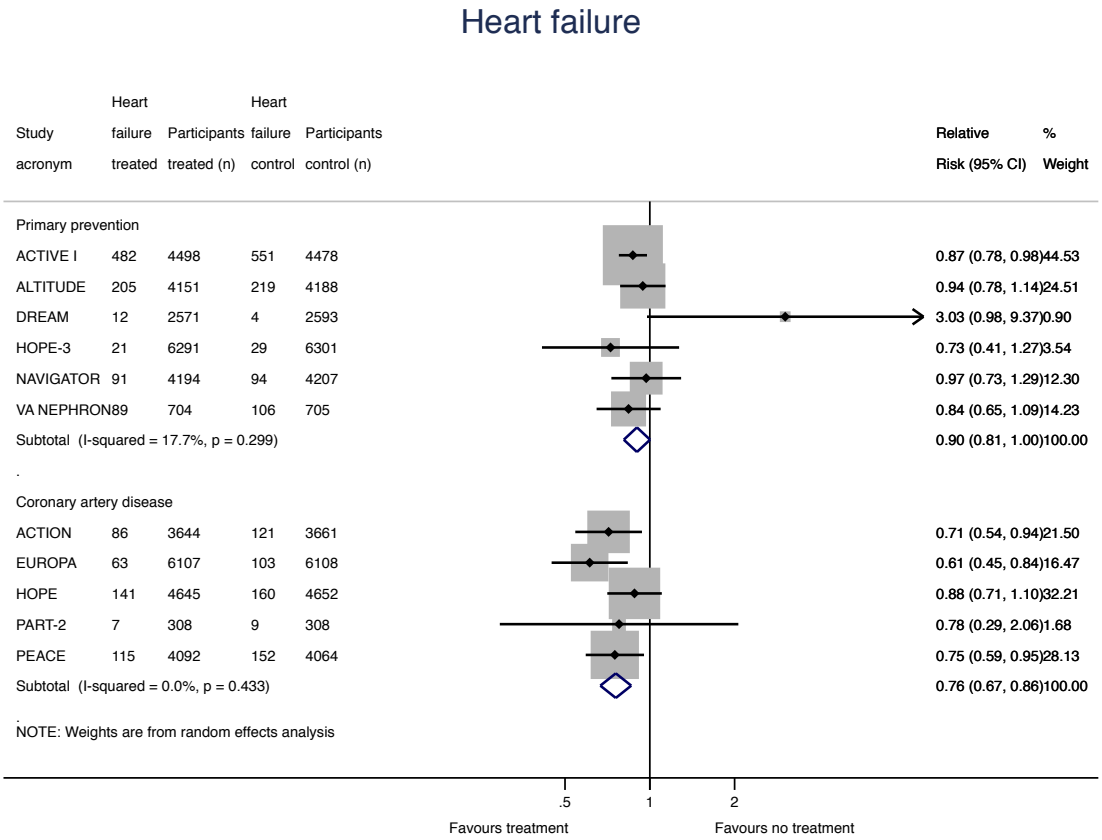
Random-effects metaregression for interaction (p=0.061)

eFigure 4 – forest plot for stroke



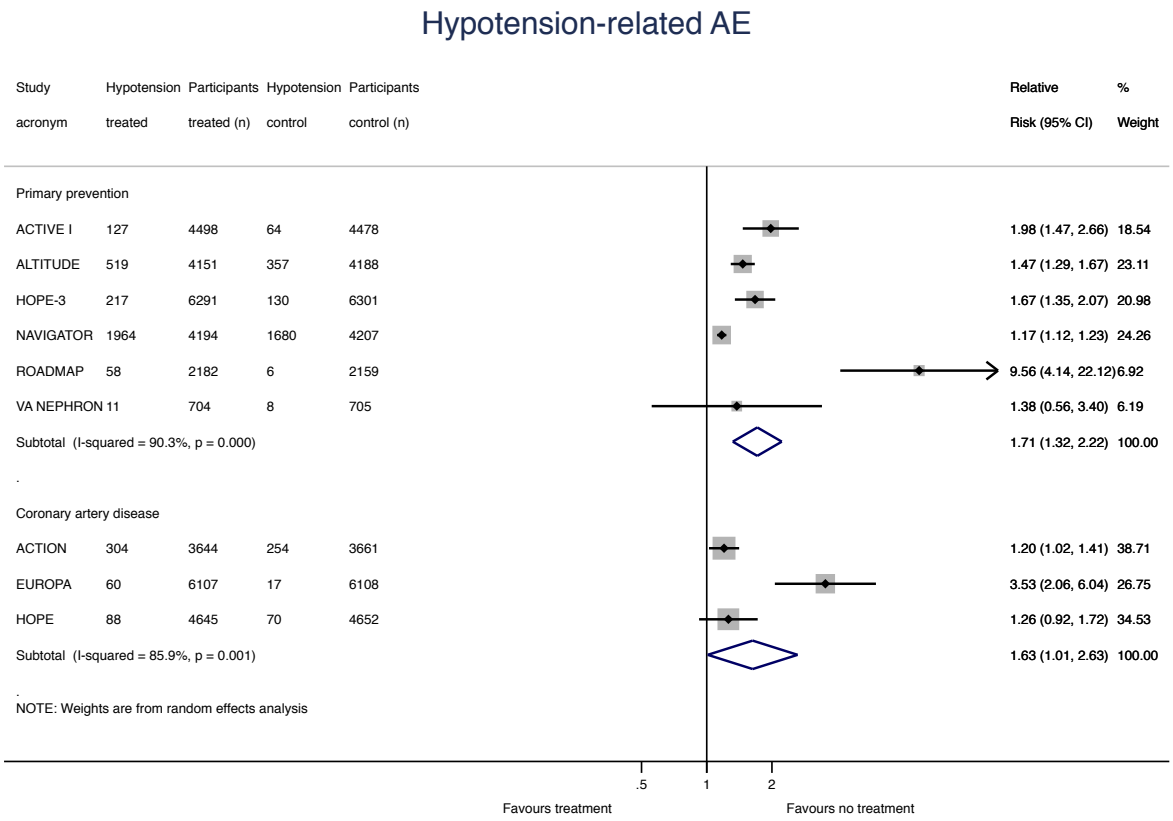
Random-effects metaregression for interaction (p=0.329)

eFigure 5 – forest plot for heart failure



Random-effects metaregression for interaction (p=0.072)

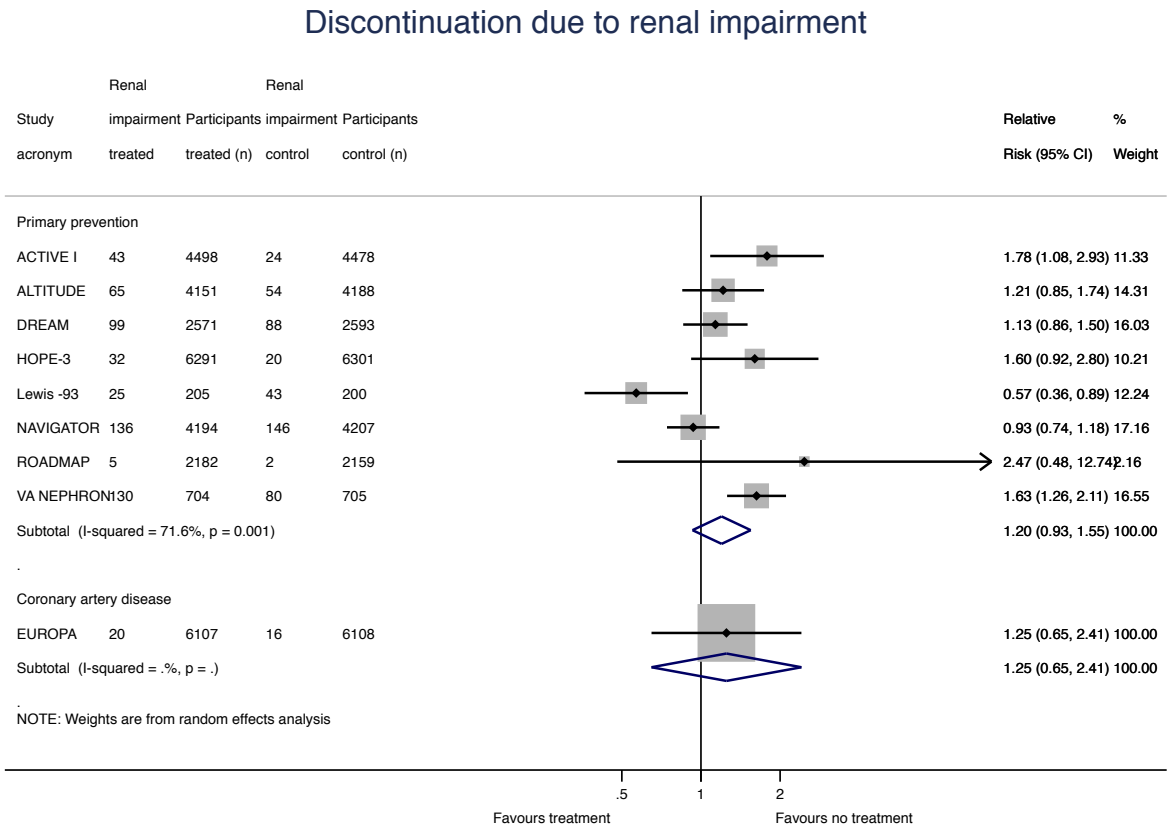
eFigure 6 – forest plot for hypotension-related AEs



AEs = adverse events

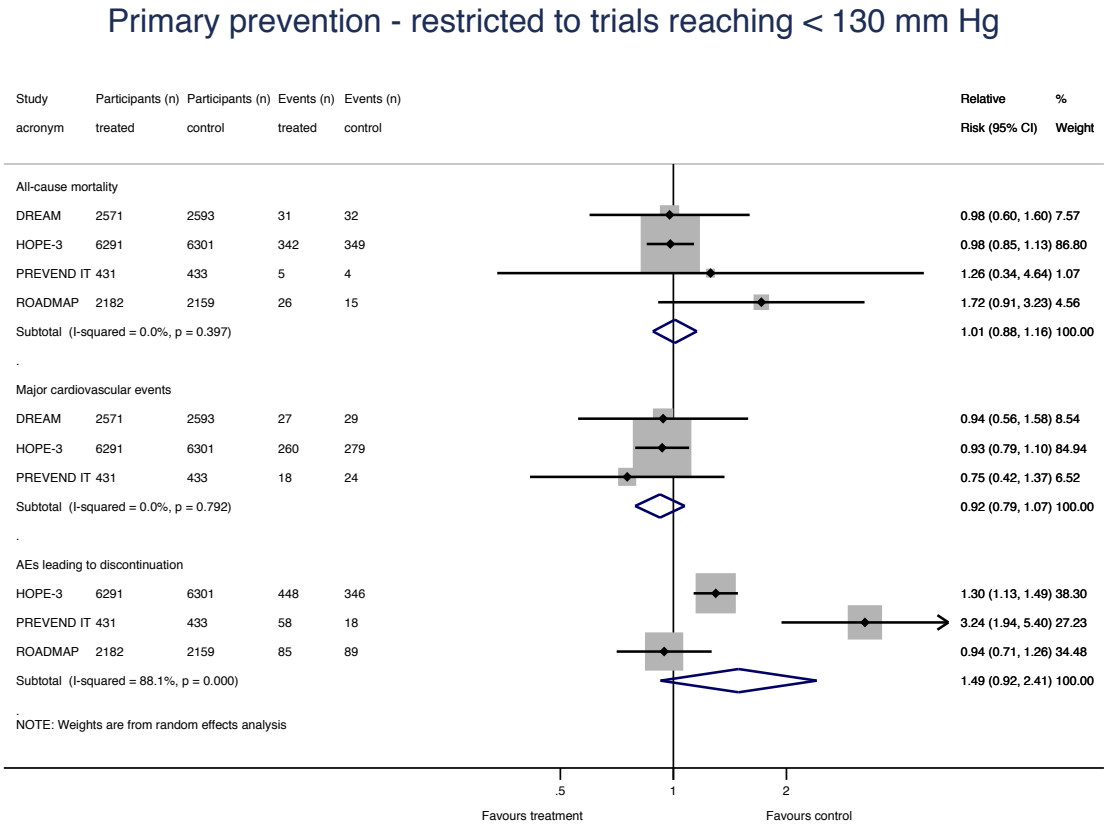
Random-effects metaregression for interaction (p=0.798)

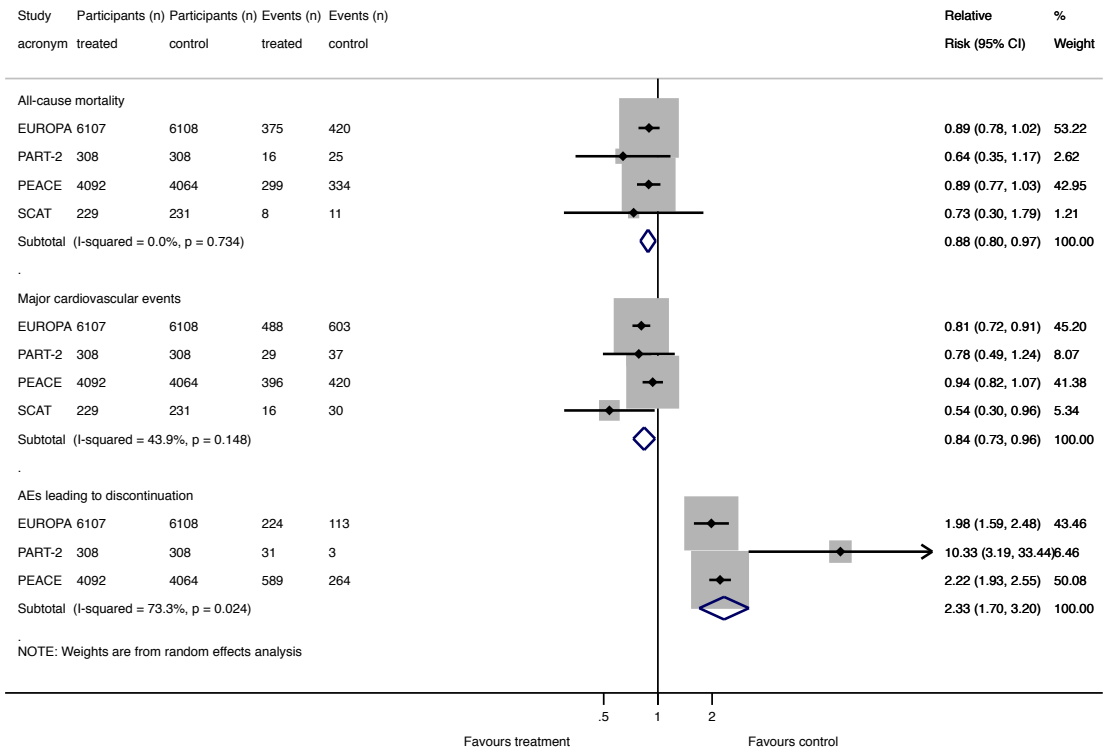
eFigure 7 – forest plot for renal impairment



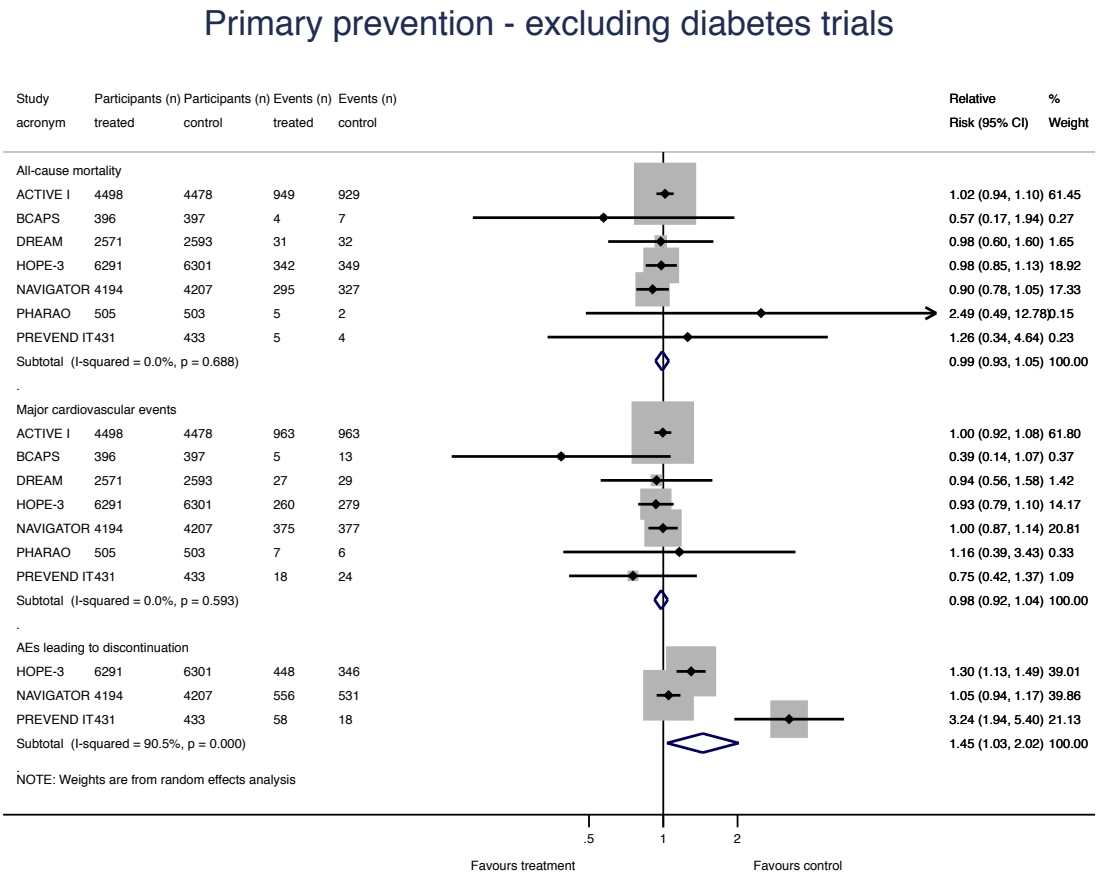
Random-effects metaregression for interaction (p=0.936)

eFigure 8 – Sensitivity analysis excluding trials not reaching < 130 mm Hg



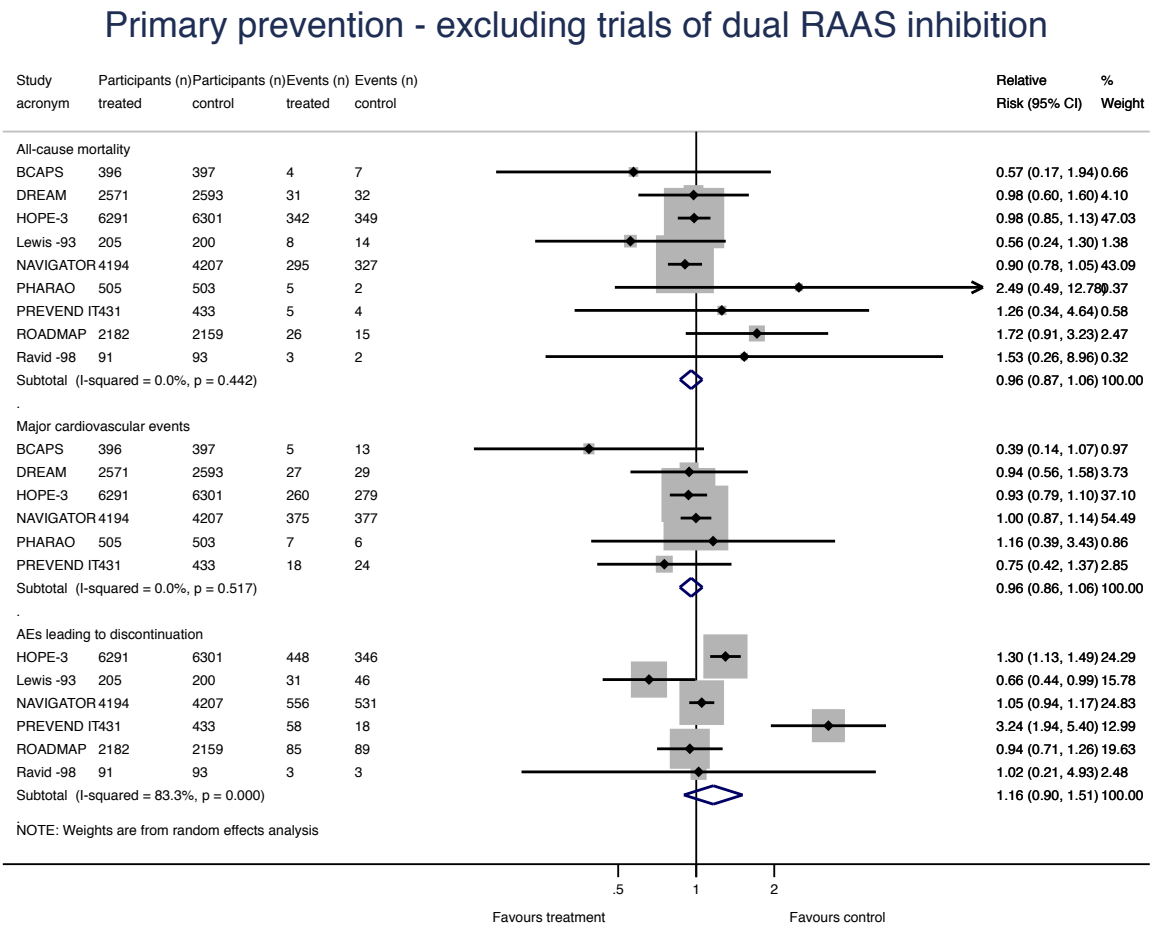


eFigure 9 – sensitivity analysis excluding trials in people with diabetes



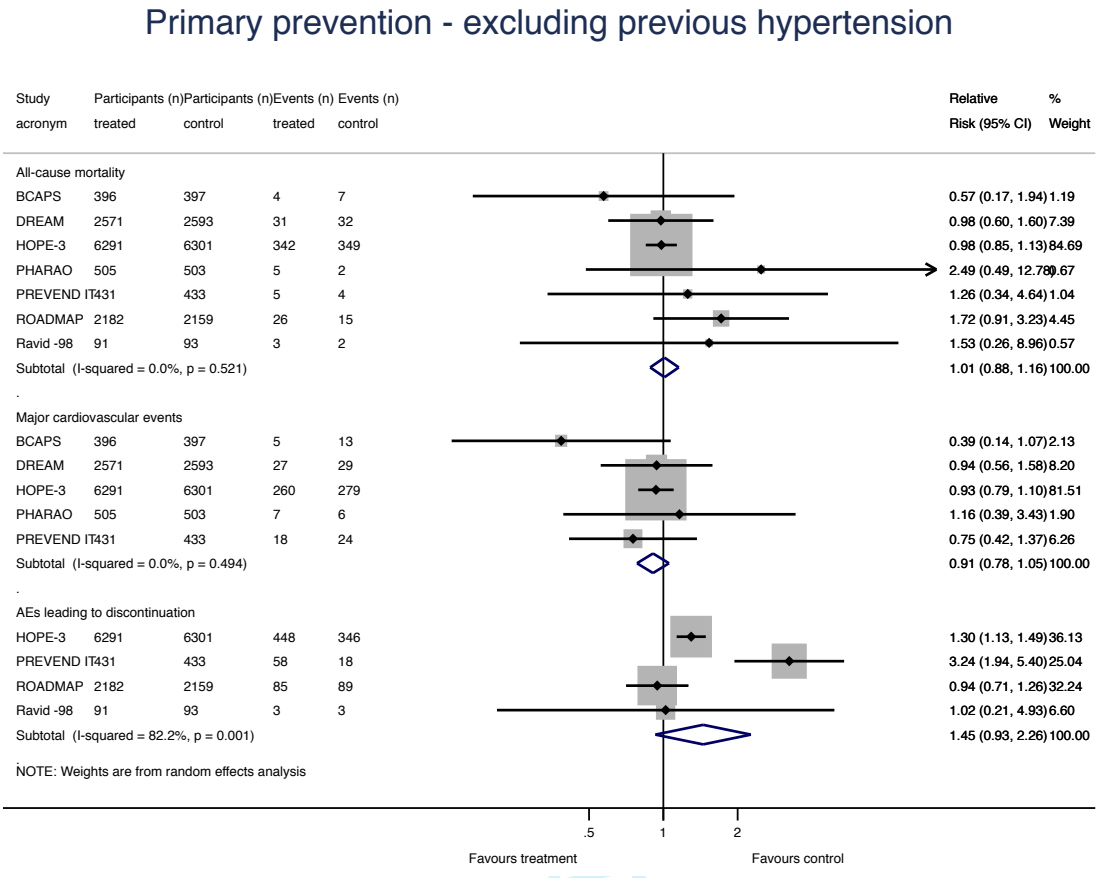
Note: None of CAD trials were primarily in people with diabetes. Hence, no sensitivity analysis was performed.

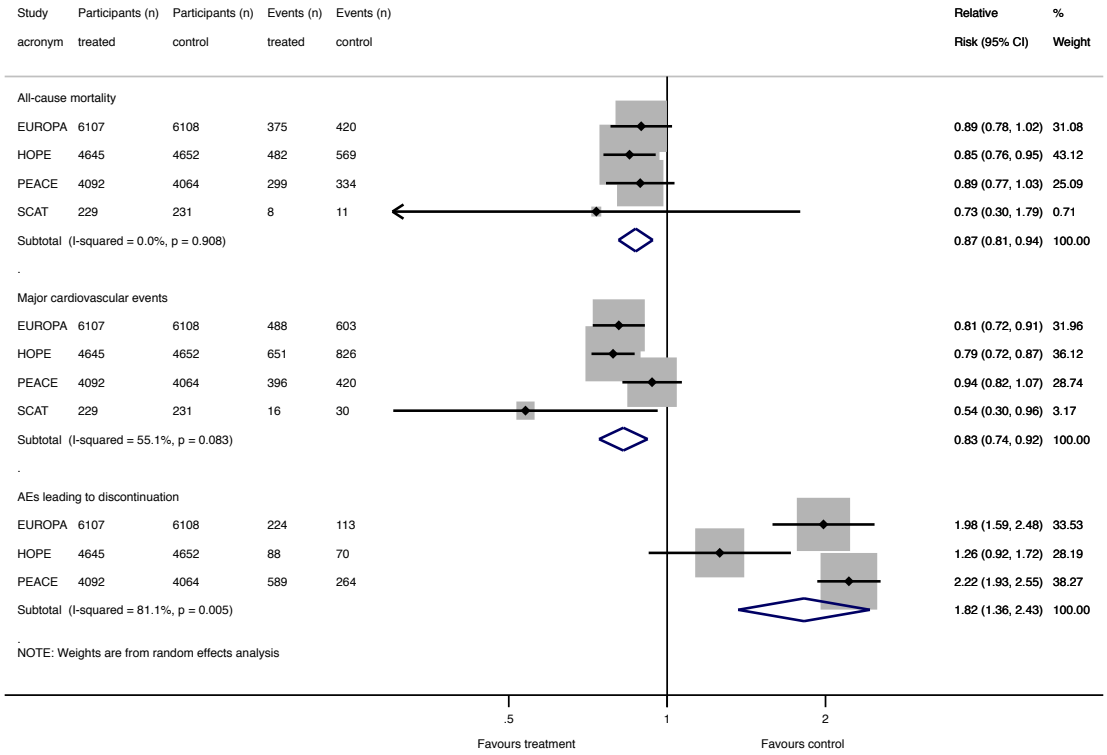
eFigure 10 – sensitivity analysis excluding trials of dual RAAS-inhibition



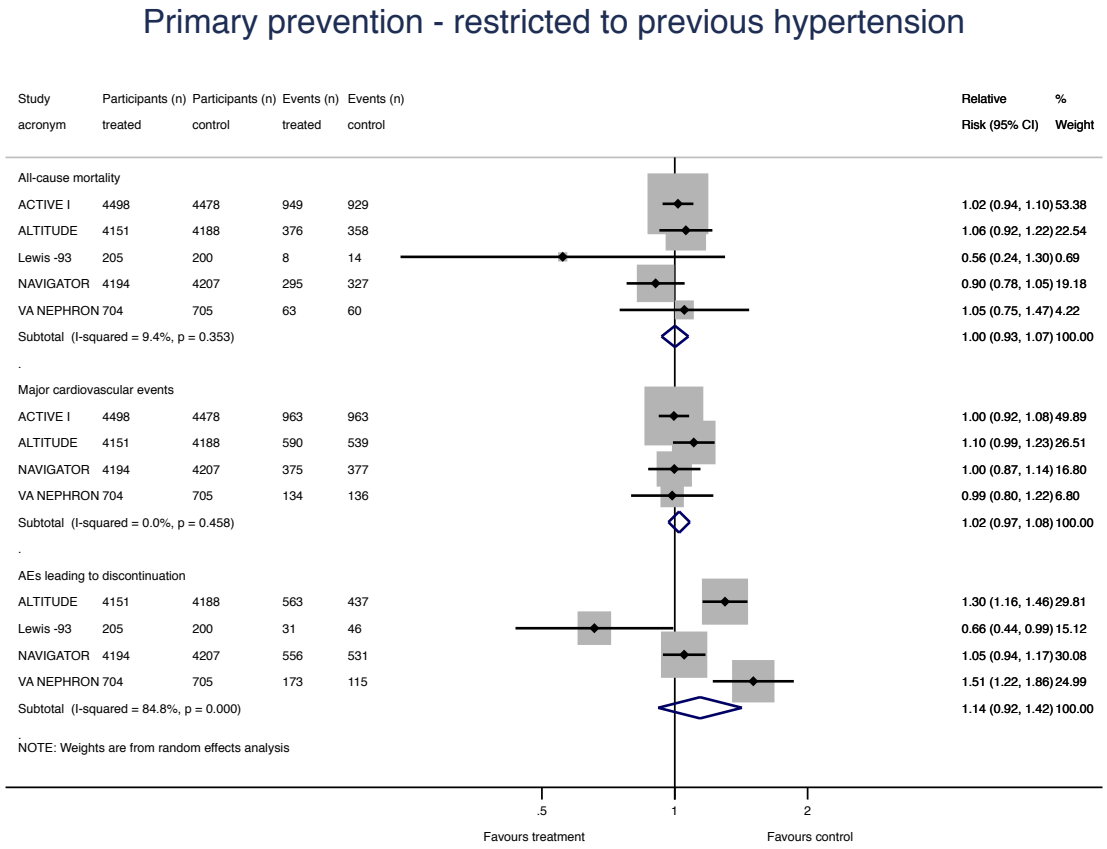
Note: None of CAD trials were testing dual RAAS inhibition. Hence, no sensitivity analysis was performed.

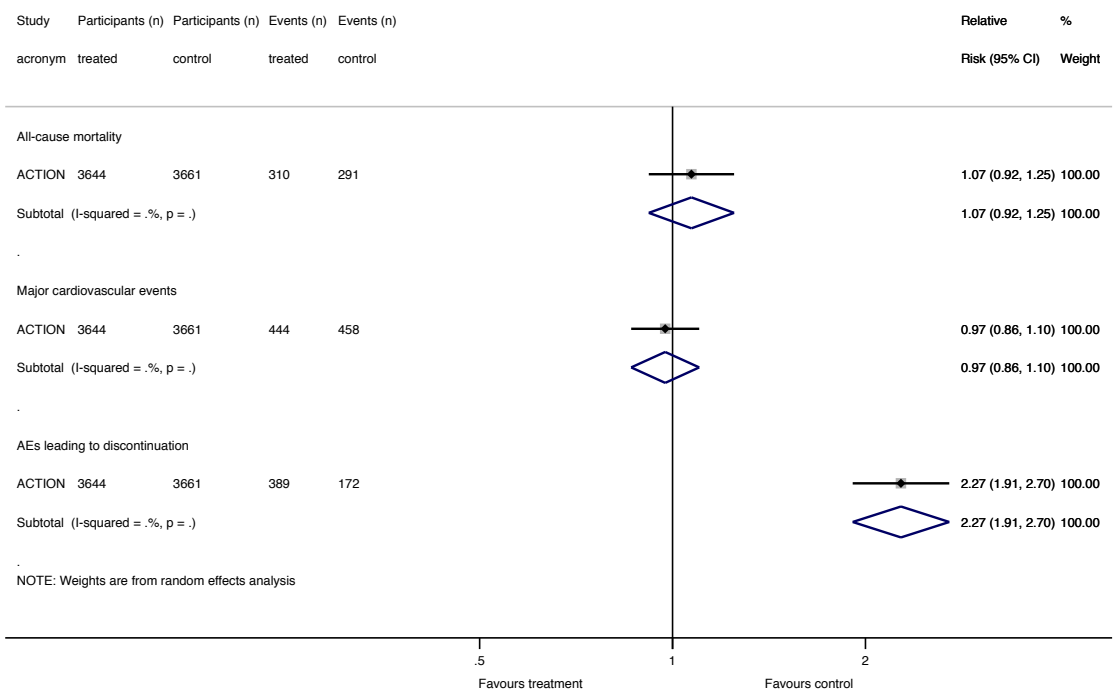
eFigure 11 – sensitivity analysis excluding trials in people with hypertension



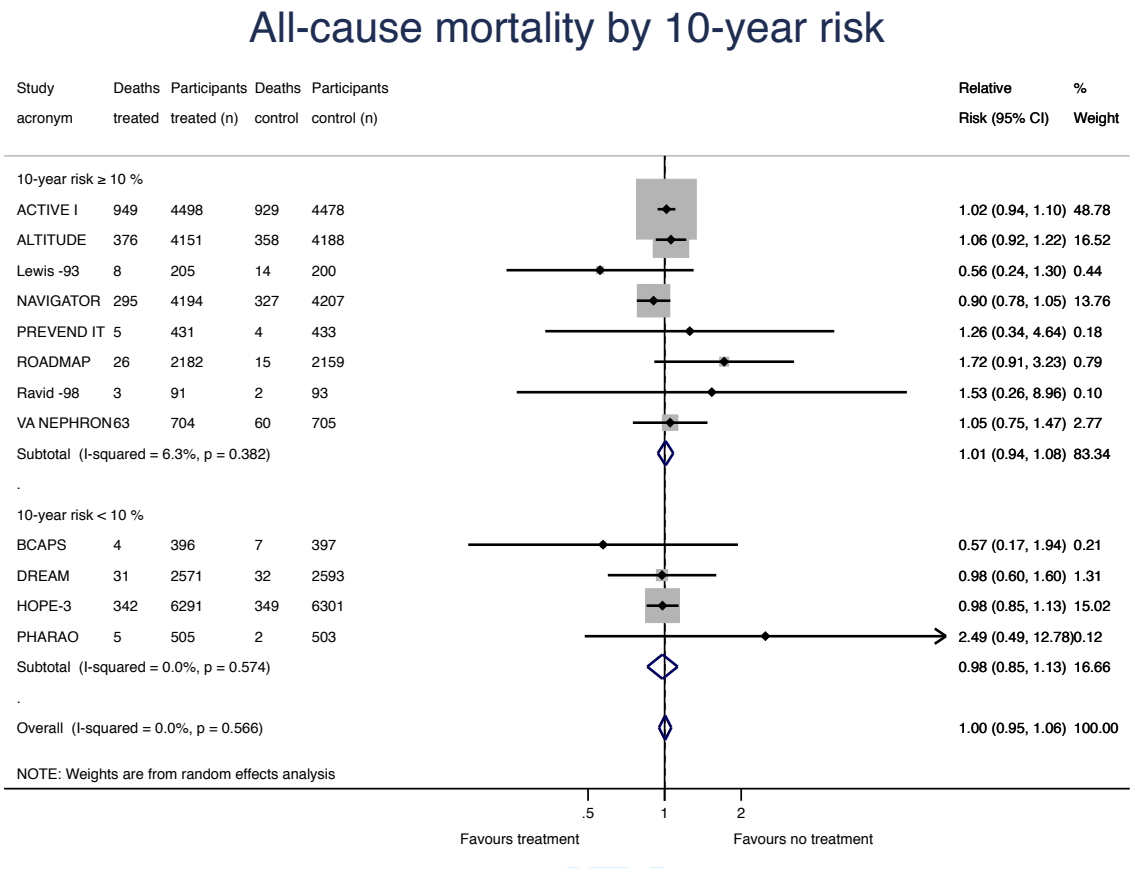


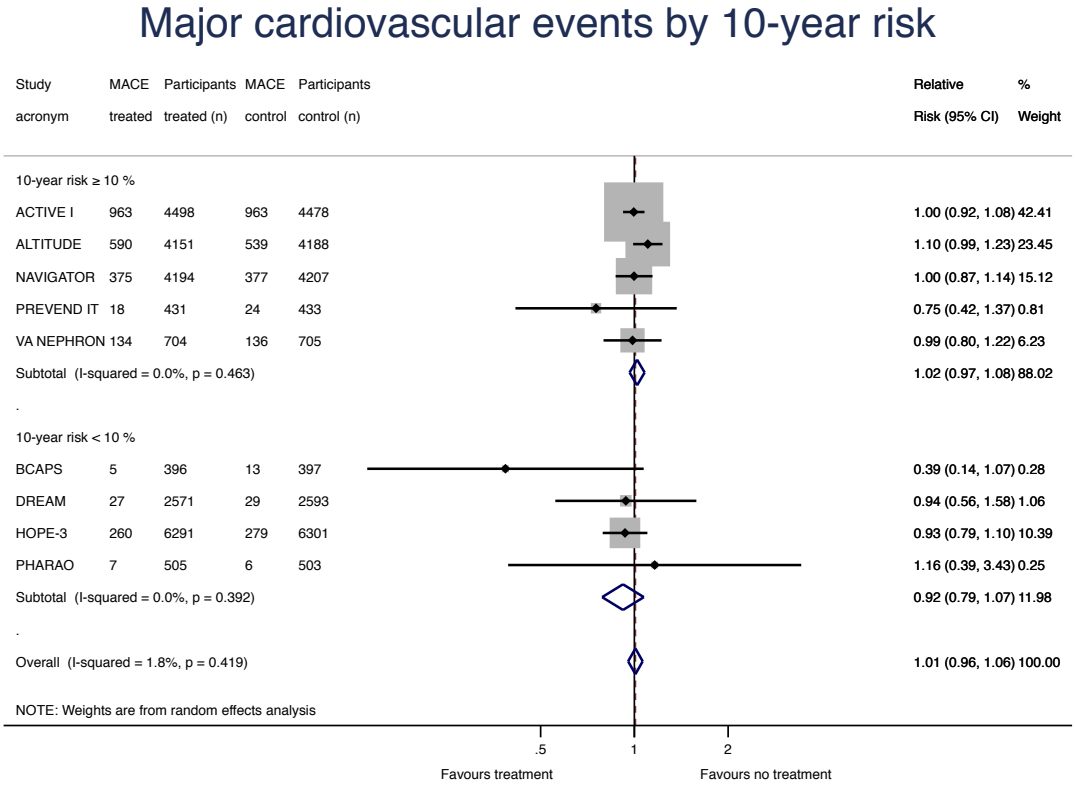
eFigure 12 – sensitivity analysis restricted to trials in people with hypertension

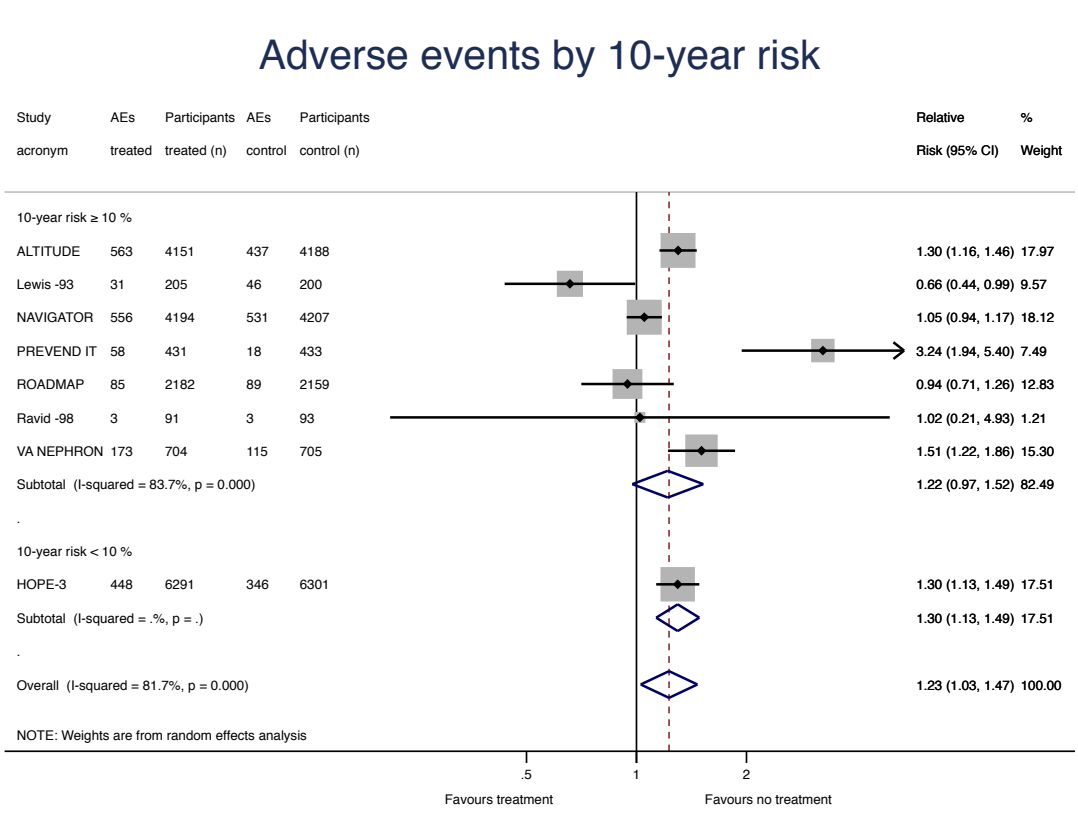




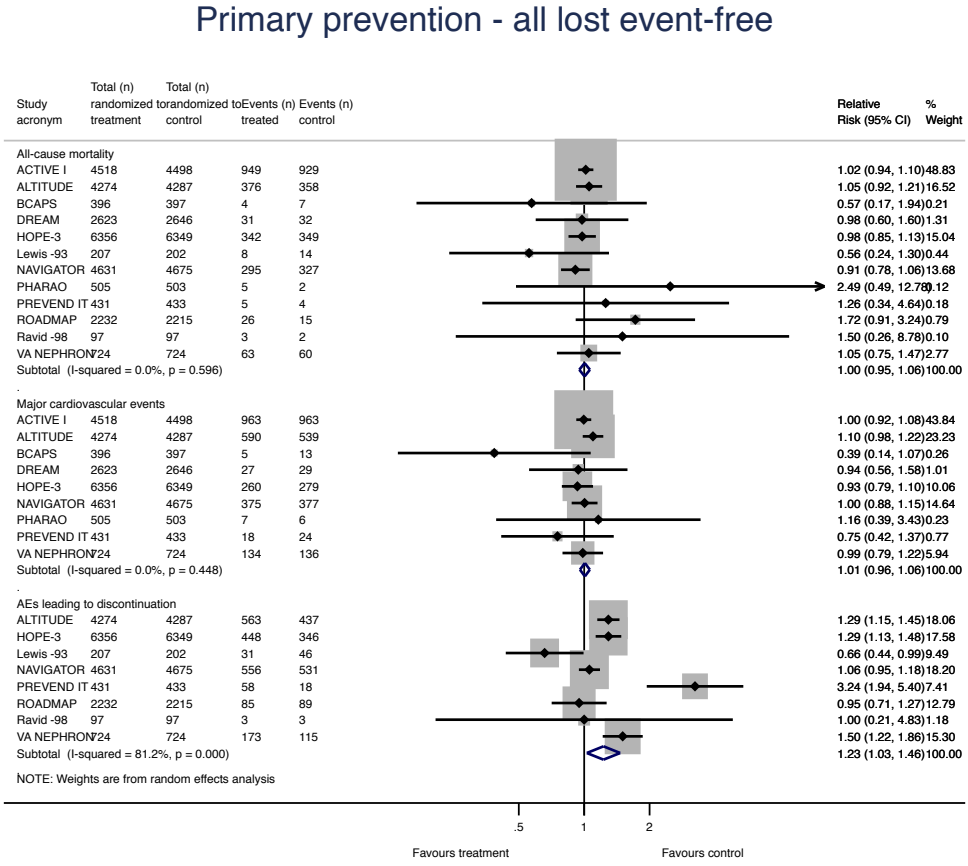
eFigure 13 – Primary preventive trials stratified by 10-year cardiovascular risk

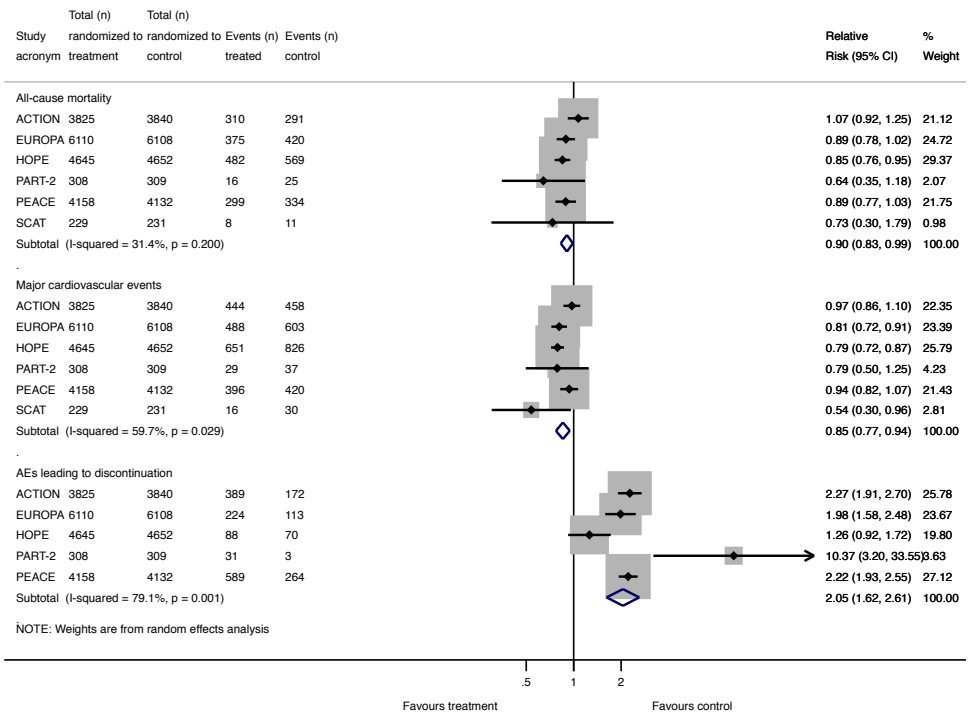




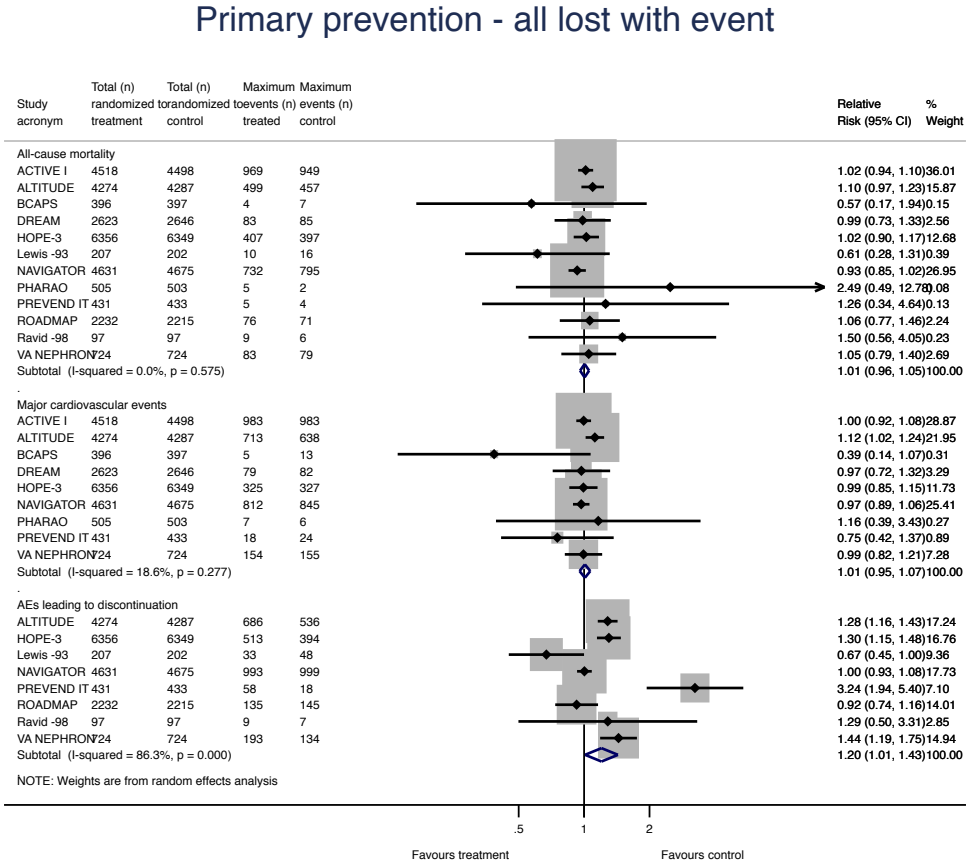

Adverse events by 10-year risk
Study acronym
AEs treated
Participants treated (n)
AEs control
Participants control (n)
Relative Risk (95% CI)
% Weight
10-year risk ≥ 10 %
ALTITUDE 563 4151 437 4188 1.30 (1.16, 1.46) 17.97
Lewis -93 31 205 46 200 0.66 (0.44, 0.99) 9.57
NAVIGATOR 556 4194 531 4207 1.05 (0.94, 1.17) 18.12
PREVEND IT 58 431 18 433 3.24 (1.94, 5.40) 7.49
ROADMAP 85 2182 89 2159 0.94 (0.71, 1.26) 12.83
Ravid -98 3 91 3 93 1.02 (0.21, 4.93) 1.21
VA NEPHRON 173 704 115 705 1.51 (1.22, 1.86) 15.30
Subtotal (I-squared = 83.7%, p = 0.000) 1.22 (0.97, 1.52) 82.49
10-year risk < 10 %
HOPE-3 448 6291 346 6301 1.30 (1.13, 1.49) 17.51
Subtotal (I-squared = .%, p = .) 1.30 (1.13, 1.49) 17.51
Overall (I-squared = 81.7%, p = 0.000) 1.23 (1.03, 1.47) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
Favours treatment
Favours no treatment

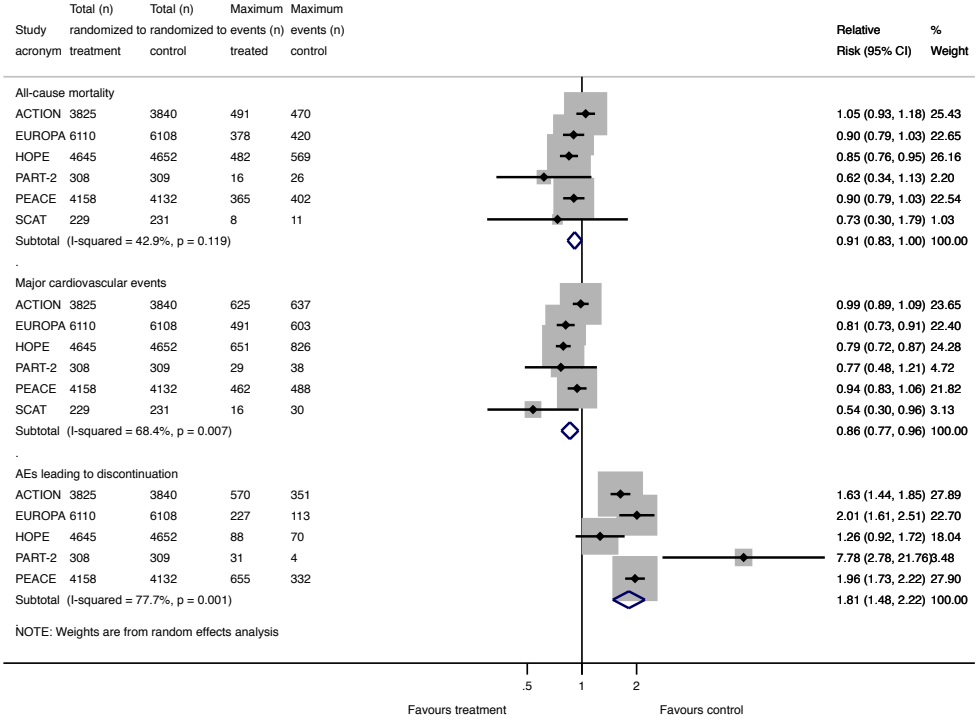
eFigure 14 - Lost to follow-up imputed as event-free



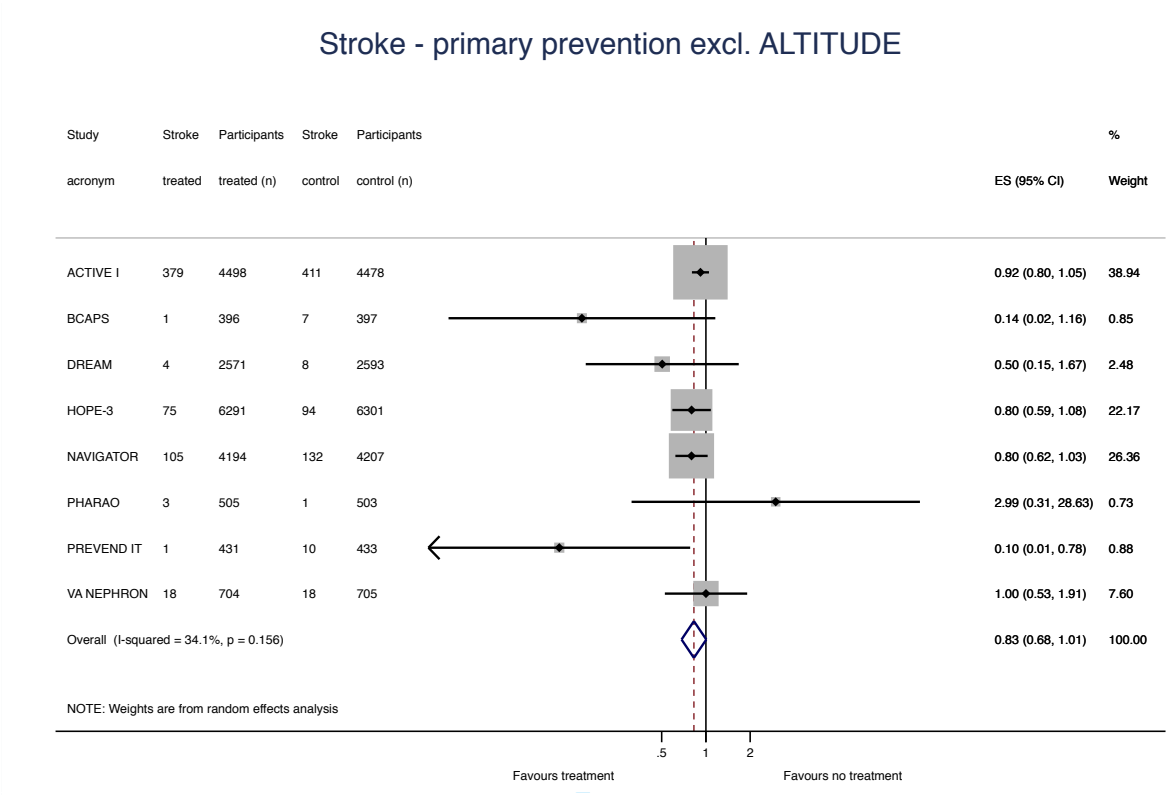


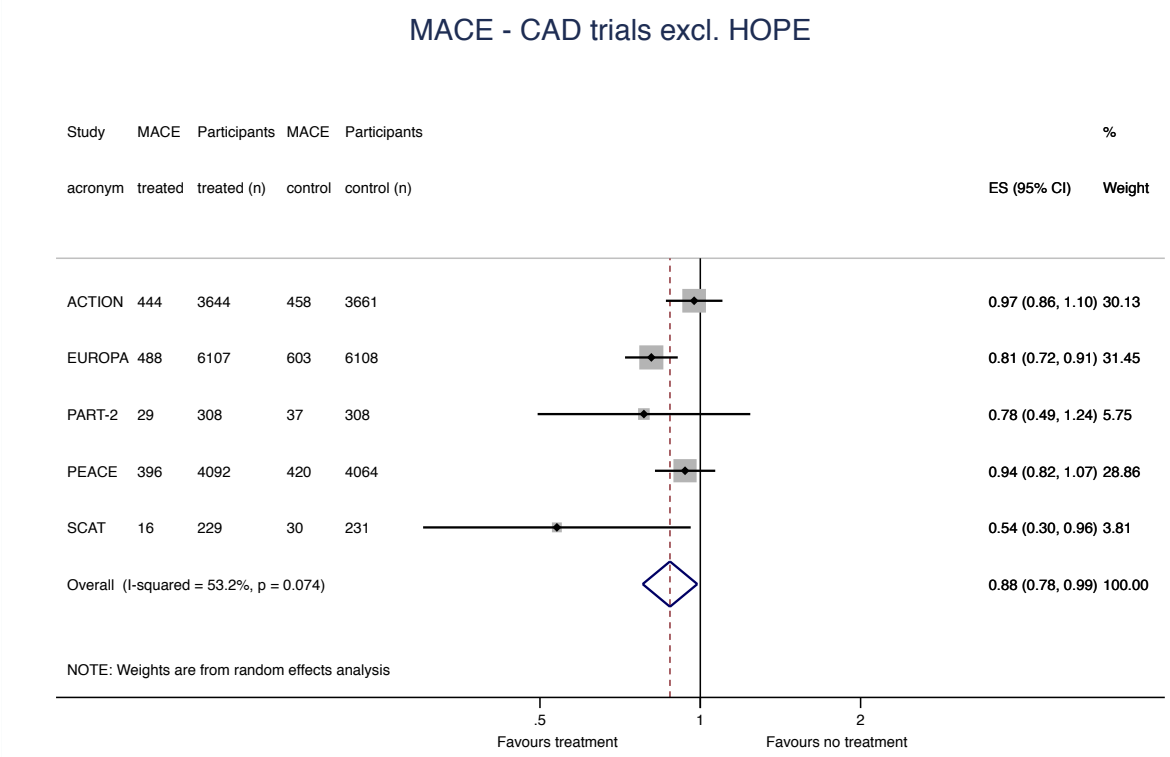
eFigure 15 - lost to follow-up imputed as having an event



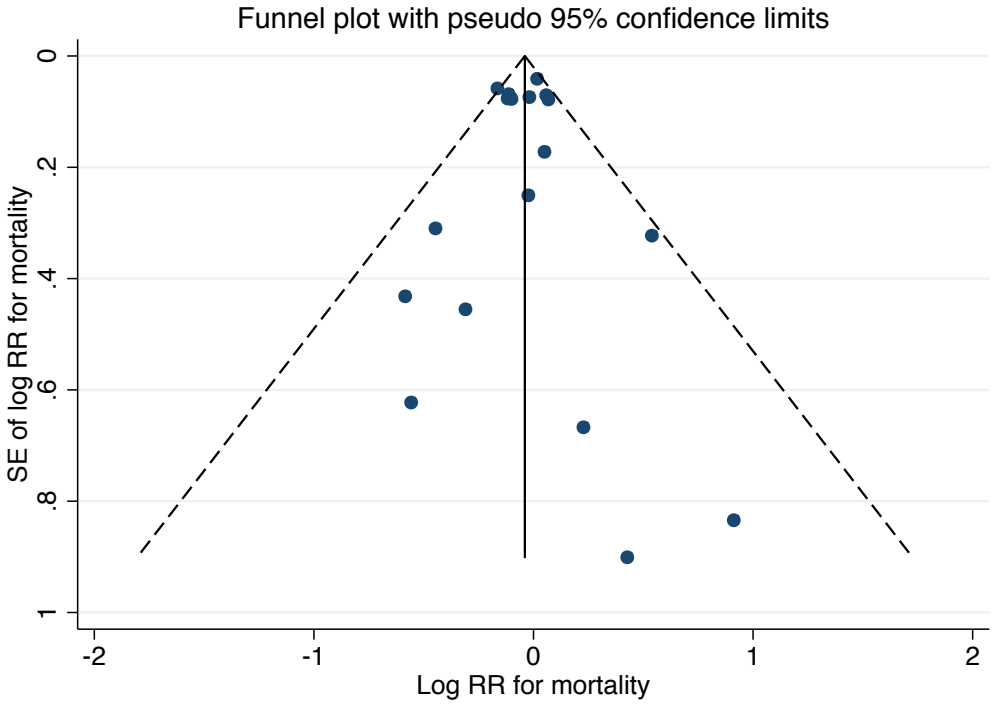


eFigure 16 - Ad hoc sensitivity analyses based on risk of bias assessment



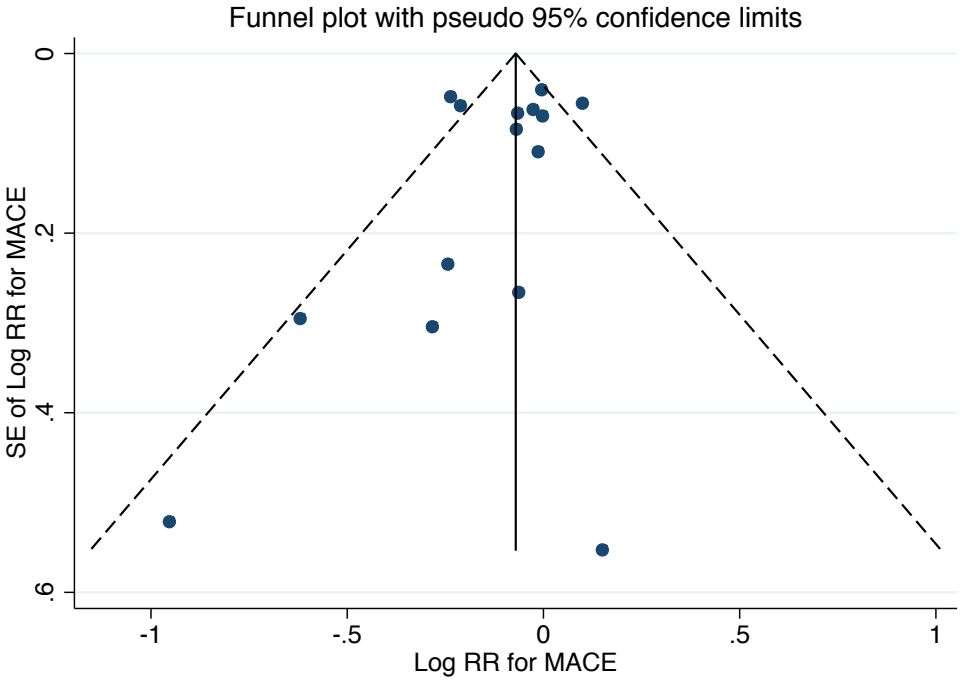


eFigure 17 – Funnel plot for all-cause mortality



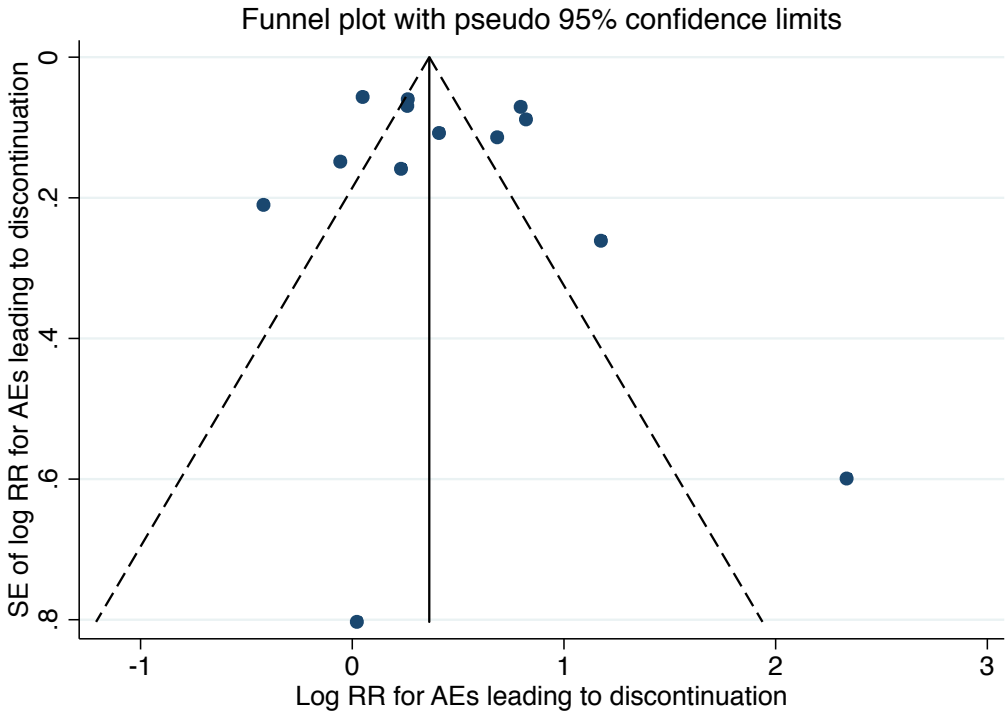
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.938

eFigure 18 – Funnel plot for major cardiovascular events



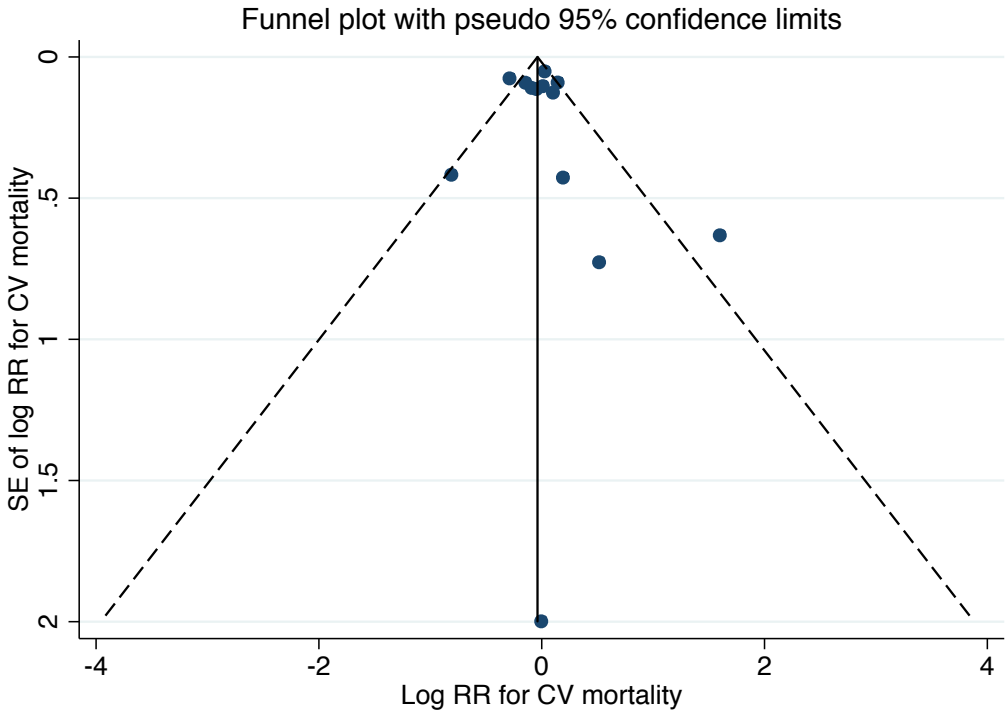
RR = relative risk. SE = standard error. MACE = major cardiovascular events.
Harbord's test for small-study effects p = 0.410

eFigure 19 – Funnel plot for adverse events leading to discontinuation



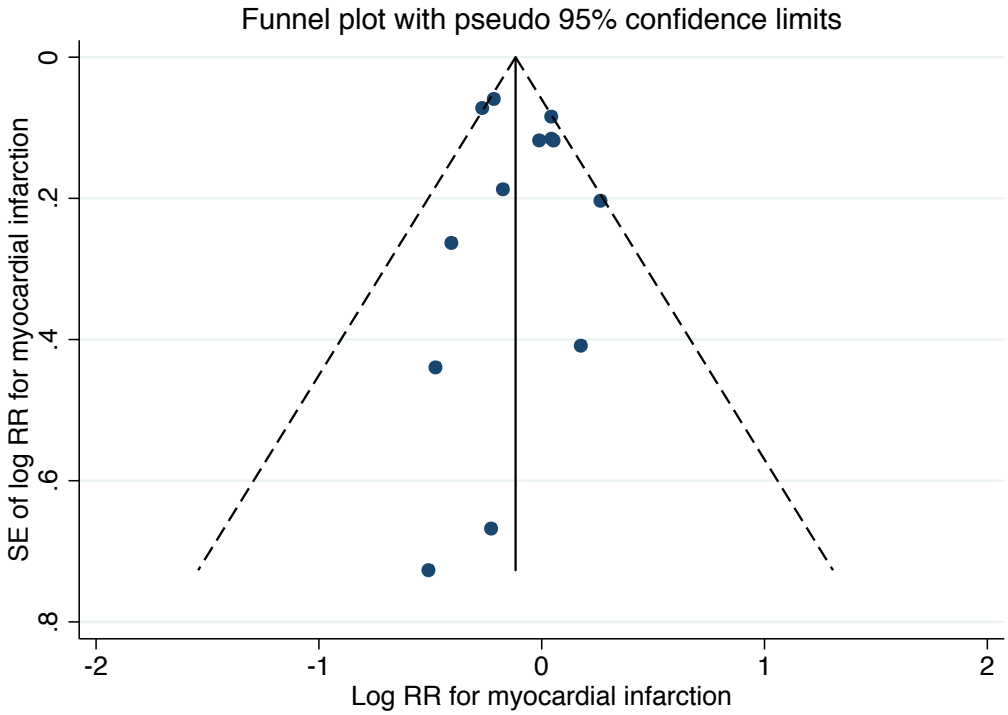
RR = relative risk. SE = standard error. AEs = adverse events.
Harbord's test for small-study effects p = 0.712

eFigure 20 – Funnel plot for cardiovascular mortality



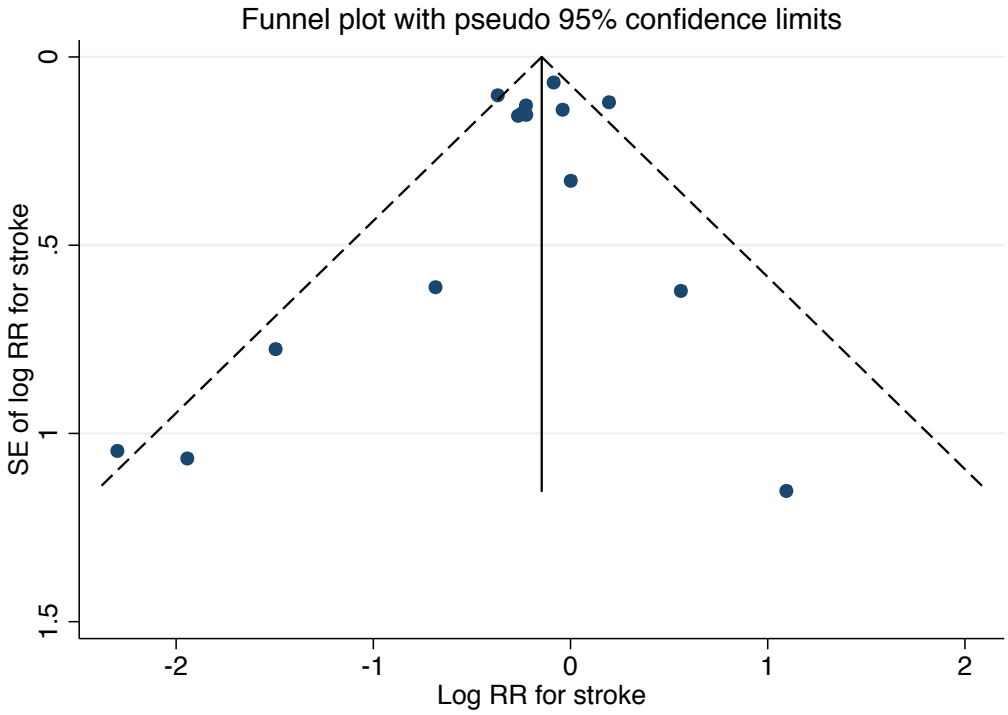
RR = relative risk. SE = standard error. CV = cardiovascular.
Harbord's test for small-study effects p = 0.507

eFigure 21 – Funnel plot for myocardial infarction



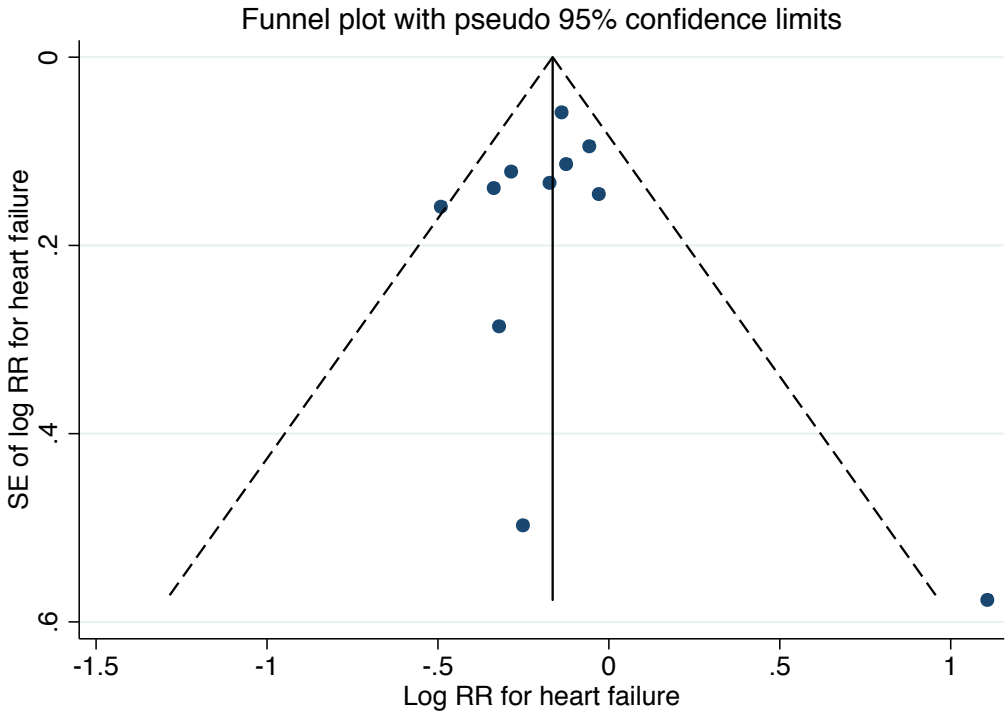
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.599

eFigure 22 – Funnel plot for stroke



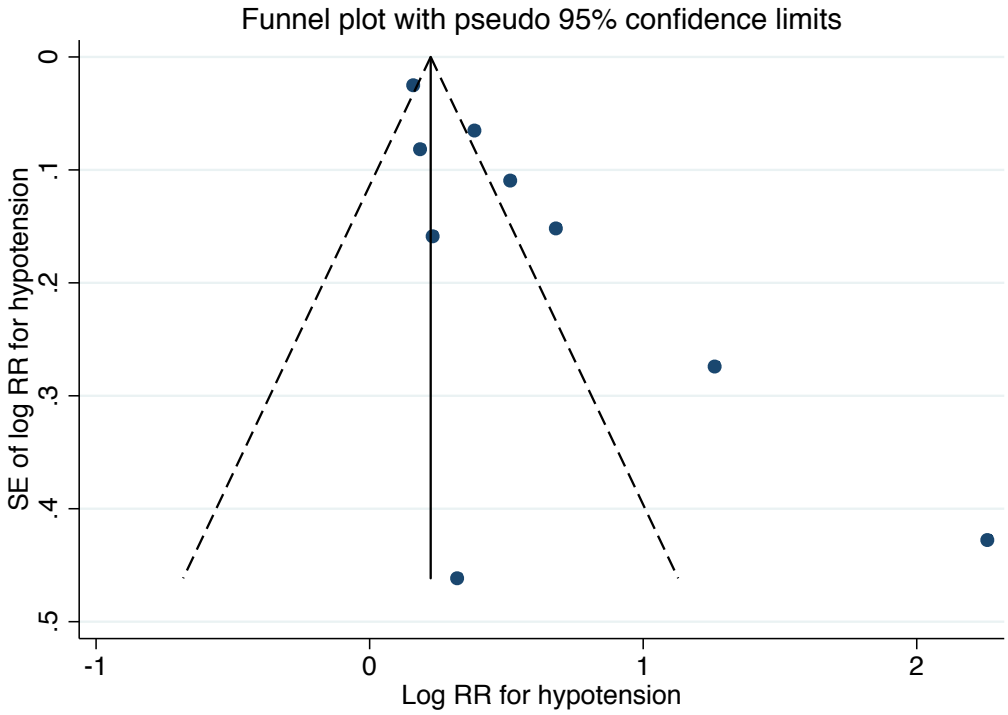
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.267

eFigure 23 – Funnel plot for heart failure



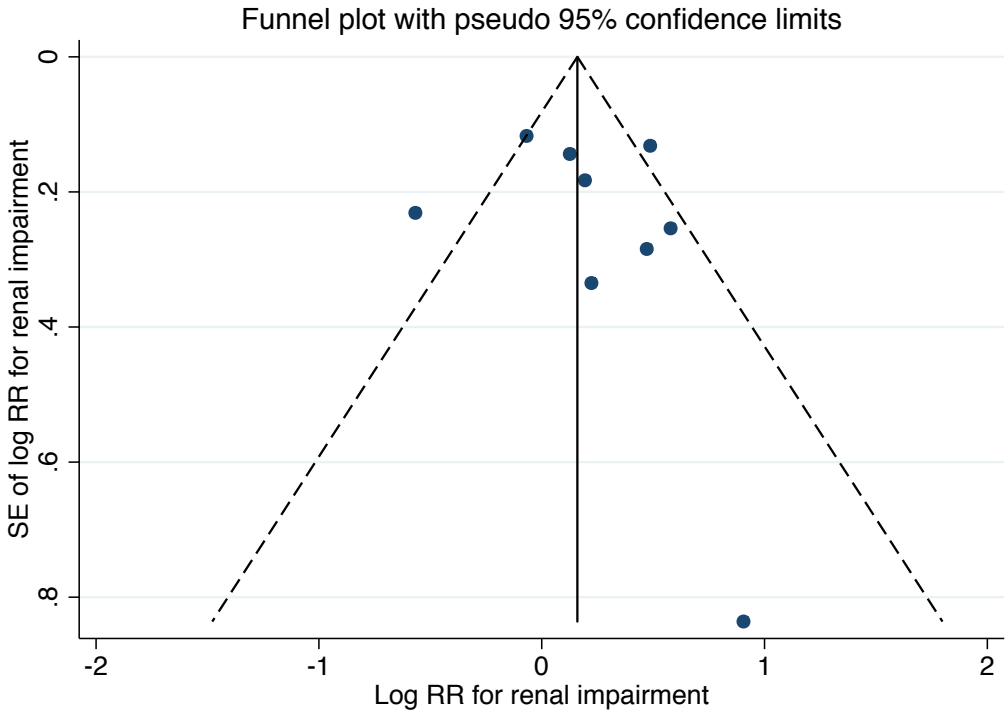
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.854

eFigure 24 – Funnel plot for hypotension-related adverse events



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.060

eFigure 25 – Funnel plot for renal impairment



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.655

eTable 1 – Studies excluded due to high risk of bias or missing data

Study ID	Reason for exclusion
DIRECT Prevent 1[1] DIRECT Protect 1[1] DIRECT Protect 2 [1,2]	Cardiovascular events were evaluated as adverse events, and therefore not blinded. Also, cardiovascular events were not followed-up in people who discontinued treatment, meaning that > 700 patients were lost to follow-up regarding these events. Based on the above, we judge the DIRECT trials to be at high risk of both detection bias and attrition bias.
EUCLID [3]	No outcome data
HDFP [4]	Patients in the intervention group and patients in the control group were treated at different clinics. We therefore judge this trial to be at high risk of performance bias.
Hunan study [5]	Original publication could not be retrieved. Data from previous meta-analyses were of uncertain quality. For example number of strokes differed by tenfold in the analyses by Ettehad et al. and Law et al. Risk of bias assessment could not be made.
INTACT [6]	No blood pressure difference between groups.
MDRD [7]	No outcome data.
NICOLE [8]	No blood pressure data.
PATS [9]	30 % of patients were lost to follow-up. This was about five times the number of events, which means this trial is at high risk of attrition bias.
STONE [10]	Randomisation likely to have failed based on large difference in number of participants in each treatment arm. We judged this trial to be at high risk of selection bias.
Suzuki -08 [11]	All patients received hemodialysis and there was no difference in blood pressure between treatment groups. Although hemodialysis was not a pre-specified exclusion criteria, it alters physiology, affecting blood pressure and drug pharmacokinetics in such a way that the results in these patients are not applicable to the general population.
Syst-China [12]	Treatment allocation was not random. Therefore this trial is at high risk of selection bias and does not fulfil the inclusion criteria of this systematic review.
USPHS [13]	> 30 % of patients dropped out, not specified how many were lost to follow-up respectively followed for outcomes. Vital status not known for 26 patients, compared to 6 deaths. This suggests high risk of attrition bias. Furthermore, treatment groups differed by 2 mm Hg in systolic blood pressure at baseline, and 60 % vs 40 % on prior antihypertensive therapy.

Note: Several of the studies presented above were outside the eligible blood pressure range. They are presented here because exclusions based of risk of bias were done before selection on blood pressure data.

eTable 2 - Absolute risk of MACE in primary preventive trials

Study ID	Pts (n)	MACE (n)	Follow-up (y)	10-year MACE-rate (%) *
ACTIVE I	9016	1926	4.1	52
ALTITUDE	8561	1129	2.7	49
BCAPS	793	18	3.0	7.6
DREAM	5269	56	3.0	3.5
HOPE-3	12705	539	5.6	7.6
Lewis -93	409	-	3.0	-
NAVIGATOR	9306	752	6.5	12
PHARAO	1008	13	3.0	4.3
PREVEND-IT	864	42	3.8	13
ROADMAP	4447	-	3.2	-
Ravid -98	194	-	6.0	-
VA-NEPHRON	1448	270	2.2	85

Pts = participants. MACE = major cardiovascular events.

* 10-year MACE-rate was calculated as (MACE/Pts)x(10/duration).

eTable 3 - Risk of bias table

Study acronym	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
ACTION [14]	Low	Low	Low	Unclear	Low	Low	Low
ACTIVE I [15]	Low	Low	Low	Low	Low	Low	Low
ALTITUDE [16]	Low	Low	Low	Low	Unclear	Low	High
BCAPS [17]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
DREAM [18]	Low	Low	Low	Low	Unclear	Low	Low
EUROPA [19]	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
HOPE [20]	Low	Low	Low	Low	Low	Low	High
HOPE-3 [21]	Low	Low	Unclear	Low	Low	Low	Low
Lewis -93 [22]	Low	Low	Low	Low	Low	High	Low
NAVIGATOR [23]	Low	Low	Low	Low	Unclear	Low	Low
PART-2 [24]	Low	Low	Low	Unclear	Low	Low	Low
PEACE [25]	Low	Low	Low	Unclear	Low	Low	Low
PHARAO [26]	Low	Low	Unclear	Low	Low	Low	Low
PREVEND-IT [27]	Low	Low	Low	Low	Unclear	Low	Low
Ravid -98 [28]	Low	Low	Low	Low	Unclear	Low	Low
ROADMAP [29]	Low	Low	Low	Unclear	Low	Low	Low
SCAT [30]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
VA-NEPHRON [31]	Low	Low	Low	Unclear	Unclear	Low	Low

eTable 4 - Hypotension-related adverse events

Study ID	Pts (n)	Events (n)	RR for hypotension
NAVIGATOR	8 401	3 644	1.17
ACTION	7 305	558	1.20
HOPE	9 297	158	1.26
VA NEPHRON	1 409	19	1.38
ALTITUDE	8 339	876	1.47
HOPE-3	12 592	347	1.67
ACTIVE I	8 976	191	1.98
EUROPA	12 215	77	3.53
ROADMAP	4 341	64	9.56

Note: the apparent asymmetry in the funnel plots is not primarily due to smaller studies having extreme results; rather studies with few events show larger relative risks. This should be interpreted cautiously, but might represent different thresholds for reporting adverse events in different trials, with larger relative risks for more severe events.

eResults - Risk of bias assessment and description

Risk of bias was judged as low when we found a clear description that fulfilled the criteria for low risk of bias according to Cochrane Collaborations risk of bias assessment tool. Risk of bias was judged as unclear if we could not find an adequate description, or if the described methods did not fulfil the criteria for either low or high risk of bias. High risk of bias was assigned when we found a description of a study characteristic of methodological feature known to be associated with biased effect estimates.

All included studies were described as randomized double-blind placebo-controlled trials. Studies judged be at unclear risk of bias for the first three domains generally provided no further description of how randomization and/or blinding was achieved, yet we have no reason to believe it failed. Trials judged to be at unclear risk of bias in the forth domain generally described that outcomes were assessed by a separate committee, but did not explicitly describe this committee as blinded.

Several trials were judged to be at unclear risk of bias for incomplete outcome data. We used this label when attrition was small and asymmetric (ALTITUDE), or when loss to follow-up-rates were higher than event-rates (others). None of the included trials had large and asymmetric loss to follow-up.

Lewis -93 reported myocardial infarction, stroke, and heart failure for both groups combined, and is therefore judged to be at high risk of bias for these outcomes. This is not likely to affect overall results, however, because Lewis -93 was a small study with very few events compared to overall analyses.

We assessed early termination, changes in protocol and sponsor involvement as other potential sources of bias. In EUROPA, the definition of the primary outcome changed during follow-up. Although this might affect the interpretation of the study findings, outcomes used in our analyses where based on pre-defined criteria and not on whether they were primary or secondary in individual studies. Thus it should have little impact on our analyses.

ALTITUDE and HOPE were stopped pre-term due to interim findings. ALTITUDE was stopped due to an increased risk of stroke in the intervention group, whereas HOPE was stopped due to decreased risk of major cardiovascular events in the intervention group. To test the impact of these trials on overall results, we performed ad-hoc sensitivity analyses where they were excluded. Exclusion of ALTITUDE from the primary preventive stroke analysis moved the estimate slightly more towards benefit (relative risk 0.83, 95 % confidence interval 0.68-1.01, compared to 0.89, 0.73-1.09 when ALTITUDE was included). Exclusion of HOPE from the MACE analysis for CAD trials moved the estimate slightly towards neutrality (0.88, 0.78-0.99, compared to 0.85, 0.77-0.94 when HOPE was included).

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8 + Suppl.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8 + Suppl.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8 + Suppl.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Suppl.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 1 & 2 Suppl.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12 Fig. 1 & 2 Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13 + Suppl.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13 + Suppl.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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Abstract

Objectives

To assess the effect of antihypertensive treatment in the 130-140 mm Hg systolic blood pressure range.

Design

Systematic review and meta-analysis.

Information sources

PubMed, CDSR and DARE were searched for systematic reviews, which were manually browsed for clinical trials. PubMed and CENTRAL were searched for trials directly in February 2018.

Eligibility criteria

Randomized double-blind trials with ≥ 1000 patient-years of follow-up, comparing any antihypertensive agent against placebo..

Data extraction and risk of bias

Two reviewers extracted study-level data, and assessed risk of bias using Cochrane Collaborations risk of bias assessment tool, independently.

Main outcomes and measures

Primary outcomes were all-cause mortality, major cardiovascular events and discontinuation due to adverse events. Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related adverse events and renal impairment.

Results

Eighteen trials, including 92 567 participants (34 % women, mean age 63 years), fulfilled the inclusion criteria. Primary preventive antihypertensive treatment was associated with a neutral effect on all-cause mortality (relative risk 1.00, 95 % confidence interval 0.95 to 1.06) and major cardiovascular events (1.01, 0.96 to 1.05), but an increased risk of discontinuation due to adverse events (1.23, 1.03 to 1.47). None of the secondary efficacy outcomes were significantly reduced, but the risk of hypotension-related adverse events increased with treatment (1.71, 1.32 to 2.22). In coronary artery disease secondary prevention, antihypertensive treatment was associated with reduced risk of all-cause mortality (0.91, 0.83 to 0.99) and major cardiovascular events (0.85, 0.77 to 0.94), but doubled the risk of adverse events leading to discontinuation (2.05, 1.62 to 2.61).

Conclusion

Primary preventive blood pressure lowering in the 130 to 140 mm Hg systolic blood pressure range adds no cardiovascular benefit, but increases the risk of adverse events. In secondary prevention benefits should be weighed against harms.

Registration

Registered in PROSPERO, registration number CRD42018088642.

Article Summary

Strengths and limitations of this study

- Meta-analysis restricted to randomized double-blind placebo-controlled trials, thereby minimizing the risk of performance bias
- Adverse events included as co-primary outcome, putting emphasis on both benefits and harms
- Separate analyses for primary and secondary preventive trials, reducing the risk of confounding from coronary artery disease and increasing the usefulness of the results in different clinical contexts
- Main limitation is the use of study-level data, with the potential for ecological bias.

Introduction

For decades, hypertension has been defined as a blood pressure (BP) ≥ 140/90 mm Hg.[1] The definition has been uniform across the world, and for most patients the recommended treatment goal has been < 140/90 mm Hg.[2-4] In 2017, the American Collage of Cardiology (ACC) and the American Heart Association (AHA) updated the U.S. guidelines, changing the definition of hypertension to ≥ 130/80 mm Hg.[5] For secondary preventive patients, and for primary preventive patients with a 10-year cardiovascular risk ≥ 10 per cent, the treatment goal is now < 130/80 mm Hg. Recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) followed, retaining the old definition of hypertension, but lowering the treatment goal to 120-130/70-80 mm Hg for most patients [6]

The revision of both sets of guidelines were heavily influenced by the Systolic Blood Pressure Intervention Trial (SPRINT).[7] SPRINT randomized > 9 000 high-risk patients (without previous stroke or diabetes) to a systolic blood pressure (SBP) target < 120 mm Hg compared to < 140 mm Hg, and was stopped preterm due to lower risk of death and cardiovascular disease in the intensive treatment group.[7] In addition to SPRINT, the ACC/AHA performed a systematic review and meta-analysis including only non-blinded randomized trials comparing different treatment goals, finding a reduced risk of major cardiovascular events and stroke in trials comparing a target ≤ 130 mm Hg to any higher target.[8]

Blinding of participants and study personnel is desirable to minimize the risk of performance bias.[9] In non-blinded studies, such as SPRINT and those included in the ACC/AHA systematic review, participants may be handled differently depending on

treatment group, thereby cofounding the assessment of the intervention. Meta-epidemiological studies have found that trials with unclear or incomplete blinding produce more favourable results compared to trials that are double-blind.[10] Additionally, in the clinic, we know the patients' blood pressure, but not what blood pressure he or she will have after adding an additional drug. Placebo-controlled trials mimic the clinical situation where the question is – should we add another drug or not?

This systematic review and meta-analysis aims to evaluate the benefits and harms associated with antihypertensive treatment in randomized double-blind placebo-controlled trials with mean SBP 130-140 mm Hg at randomization. Such an approach eliminates the risk of performance bias, yet produces treatment effect estimates reasonably specific for the SBP interval for which the new recommendations differ from previous ones. Because the ACC/AHA systematic review was restricted to non-blinded target trials and this review is restricted to placebo-controlled trials of different agents, our analyses serves as validation of the ACC/AHA systematic review findings in a different population with theoretically more robust methods.

Methods

We performed a systematic review and meta-analysis guided by the recommendations from the Cochrane Collaboration.[9] A protocol was registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42018088642. Reporting follows the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Studies were eligible if they were randomized double-blind placebo-controlled trials with ≥ 1000 patient-years of follow-up; assessing the effect of any antihypertensive agent against placebo, with mean baseline SBP ≥ 130 mm Hg and < 140 mm Hg. The 1000 patient-year cut-off was chosen to reduce the risk of small-study bias. Target-driven trials were excluded due to reasons described above, and trials comparing different antihypertensive agents against each other were excluded because they risk assessing blood pressure-independent effects of agents. [9,10] We also excluded trials in patients with acute myocardial infarction or heart failure/left ventricular dysfunction because several antihypertensive agents are thought to affect on clinical outcomes through blood pressure-independent mechanisms, like reduced preload, reduced afterload and sympathetic inhibition, in these settings.[12,13]

We used one of our recent, more comprehensive systematic reviews, assessing treatment effect of antihypertensive treatment across blood pressure levels in a wide range of patient categories, for study selection.[14] Search strategies for the previous review are presented in the online supplement (eMethods). In addition, we searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from the date of the previous search until February 2018, using search terms ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke). Titles were screened by M.B. and apparently irrelevant publications were removed. Two authors judged abstracts separately, after which final decision on eligibility was reached through discussion (eFigure 1).

Data were extracted from the included studies into specially designed Excel sheets by two authors separately. When extracted data differed between authors, we revisited

original publications. Descriptive data were collected on study level, whereas blood pressure data and outcome data were collected for each treatment group individually. All trials were judged for risk of bias by two authors separately, using Cochrane Collaboration´s Risk of Bias assessment tool.[15] The risk of bias tool covers six specific domains related to randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, attrition and outcome reporting. Also, we assessed sponsor involvement, protocol changes and premature study discontinuation as other potential sources of bias. Trials judged to be at high risk of selection bias, performance bias, detection bias or attrition bias (first five domains), were excluded from all analyses (eTable 1). Risk of bias for selective reporting should be considered interpreting the overall analyses for each outcome rather than individual trials, because lack of data, rather than biased data, may produce biased overall results.[9, 15]

Primary outcomes were all-cause mortality, MACE (defined as cardiovascular death, myocardial infarction and stroke if not specified otherwise), and discontinuation due to adverse events (AEs). Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related AEs, and discontinuation due to renal impairment/acute kidney injury.

Results were analyzed according to the intention-to-treat principle, in the sense that participants were analyzed in their assigned treatment group. When study participants were lost to follow-up, relative risks (RR) were calculated using complete cases in the denominator, according to the recommendations from the Cochrane Collaboration.[9] In two sets of sensitivity analyses, we calculated RRs using the observed number of events in the numerator and the total number of randomized participants in the denominator

(assuming that all participants lost to follow-up were event free), and the observed number of events plus number of participants lost to follow-up in the numerator and the total number of randomized participants in the denominator (assuming that all participants lost to follow-up had experienced an event). RRs were not standardized for BP differences in trials, because such standardization is associated with increased heterogeneity, unbalanced study weights, and biased overall results.[16]

Relative risks from individual trials were pooled using DerSimonian-Laird random-effects meta-analyses. We separated primary preventive studies from studies in people with established coronary artery disease (CAD), because these represent clinically different populations, and because we have previously observed potentially different treatment effects in these groups.[14] Trials with mixed populations were classified as CAD trials if ≥ 50 % of participants had previous CAD. Treatment effect interaction between primary preventive studies and CAD studies was assessed using random-effects metaregression. Pre-specified sensitivity analyses, excluding trials in people with diabetes, trials of dual renin-angiotensin-aldosterone system (RAAS) inhibition, trials not reaching < 130 mm Hg in the intervention group, trials of previously treated/hypertensive patients, and trials of treatment naïve patients, were performed to test the impact of different patient/trial characteristics on overall results for primary outcomes. We explored potential effect modification by diabetes and absolute cardiovascular risk as continuous explanatory variables using random-effects metaregression. Lastly, we performed ad-hoc subgroup analyses, stratifying primary preventive trials by 10-year MACE event-rate above versus below 10 %, to approximate the cut-off used in the 2017 ACC/AHA guidelines.[5]

Between-study heterogeneity in meta-analyses was assessed calculating I-squared, which represents the percentage of variance between studies that cannot be explained by chance alone. When statistical heterogeneity was present we sought for corresponding clinical heterogeneity. If statistically deviating studies differed with respect to clinical characteristics, they were excluded in sensitivity analyses. Small-study effects were assessed through funnel plots for all primary and secondary outcomes, using Harbord´s test for asymmetry.[17] All analyses were performed using STATA v12.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advice on interpretation or writing up of results. Since we used only aggregated data from previous trials, we are unable to disseminate the results of the research to study participants directly.

Results

Eighteen trials[18-35], including 92 567 participants (34 % women; mean age 63 years), fulfilled the inclusion criteria (table 1). During an average of 4.5 years under randomized double-blind treatment, 2 042 participants were lost to follow-up (2.2 %), resulting in 90 525 complete cases and 407 000 patient-years of follow-up. Twelve trials[19-22,25-27,30-33,35], including 54 020 participants, were classified as primary preventive. Mean baseline SBP in primary preventive trials was 138 mm Hg, mean follow-up SBP was 132 mm Hg respectively 135 mm Hg with active treatment versus

placebo, with a weighted mean difference between groups of 3.4 mm Hg. Six trials[18,23,24,28,29,34], including 38 547 participants, were classified as CAD trials; mean baseline SBP was 137 mm Hg, mean follow-up SBP was 130 mm Hg in the active treatment group, 134 mm Hg in the placebo group, with 4.2 mm Hg difference between groups.

In primary prevention (figure 1), treatment was not associated with any effect on all-cause mortality (relative risk 1.00, 95 % confidence interval 0.95 to 1.06) or MACE (1.01, 0.96 to 1.05), but an increased risk of AEs leading to discontinuation (1.23, 1.03 to 1.47). In CAD trials (figure 2), treatment reduced the risk of all-cause mortality by 9 % (0.91, 0.83 to 0.99), and the risk of MACE by 15 % (0.85, 0.77 to 0.94), but doubled the risk of AEs leading to discontinuation (2.05, 1.62 to 2.61). Heterogeneity was low in mortality and MACE analyses for primary prevention, moderate to high in CAD trials, and very high for AEs in both cohorts. The difference between primary preventive trials and CAD trials was significant for MACE (p=0.019) and borderline for all-cause mortality and AEs (p=0.051 respectively 0.070).

None of the secondary efficacy outcomes were affected by primary preventive treatment (table 2; online supplement eFigure 2-7). Hypotension-related AEs increased by 71 % (1.71, 1.32 to 2.22) whereas discontinuation due to renal impairment showed a non-significant tendency towards harm (1.20, 0.93 to 1.55). Of note, heterogeneity was high in the renal impairment analysis, mostly due to one study in patients with type 1-diabetes and macroalbuminuria.[26] When this study was removed in a sensitivity analysis, heterogeneity decreased and the observed risk increase became nominally significant (1.30, 1.06 to 1.58).

In CAD trials (table 2; online supplement eFigure 2-7), treatment reduced the risk of myocardial infarction (0.83, 0.72 to 0.97), stroke (0.79, 0.66 to 0.94), heart failure (0.76, 0.67 to 0.86), and cardiovascular death (0.86, 0.74 to 1.00, p=0.047). Differences between primary prevention and CAD trials were significant or borderline significant for all efficacy outcomes except stroke (eFigure 2-7). The relative risk of adverse events was similar as in primary preventive studies, although estimates were less precise and reporting was poor (only one trial reported renal impairment).

Sensitivity analyses, testing the impact of different trial characteristics, shifted effect estimates slightly (eFigure 8-12), but not enough to affect the interpretation of our main findings. Metaregression analyses, exploring potential effect modification by observed cardiovascular risk and diabetes mellitus were non-significant. Both sensitivity analyses and metaregression analyses should be interpreted carefully due to small number of trials. Of note, the absolute 10-years risk of MACE was well above the 10% threshold for recommending treatment in the ACC/AHA guidelines, with an average risk across studies of 26 % (eTable 2); subgroup analyses of primary preventive trials stratified by 10-year cardiovascular event-rate found no interaction between risk of MACE and treatment effect (eFigure 13).

Risk of bias was generally judged as low for individual trials (eTable 3 & eResults). We required studies to be described as randomized double-blind placebo-controlled trials to be eligible. Loss to follow-up was limited, and sensitivity analyses imputing all participants lost to follow-up as either having an event or being event-free did not alter effect estimates (eFigure 14-15). Three trials were judged to be at high risk of bias for

individual domains.[20,24,26] We performed sensitivity analyses, testing the impact of these trials on our primary outcomes (eFigure 16). This had marginal effects on relative risks and confidence intervals, but no effect on nominal significance for any analysis.

Funnel plots showed no signs of asymmetry (eFigure 17-25), although such analyses should be interpreted carefully due to the small number of trials. The possible exception was hypotension-related adverse events where interaction was borderline significant despite low statistical power (p=0.06). When we explored this further, we found that treatment effect correlated with number of events but not study size (eTable 4). The frequency of hypotension-related AEs varied by a factor of 50 between trials, presumably representing different thresholds for reporting. Thus, the observed association between number of adverse events and the relative risk of adverse events might represent a stronger association between treatment and severe events compared to less severe events.

Discussion

This systematic review and meta-analysis evaluates if antihypertensive treatment in the 130-140 mm Hg SBP interval is supported by findings from randomized double-blind placebo-controlled trials. This does not seem to be the case in primary prevention, with no treatment effect on all-cause mortality or MACE, but an increased risk of AEs leading to discontinuation. In people with previous CAD, treatment might be beneficial, though these findings should be interpreted more cautiously due to statistical heterogeneity and wider confidence intervals. While the type of trials included here do not assess SBP targets by design, they correspond to the clinical situation of adding an extra pill to

patients with a SBP between 130 and 140 mm Hg. Overall, the results presented here do not support such treatment, except for in patients with established CAD.

This paper has several important limitations that need to be addressed. Firstly, we only had access to aggregated data, making analyses susceptible to ecological bias. Studies were included based on average SBP levels, meaning that individual participants with an SBP > 140 mm Hg or < 130 mm Hg were included in the analyses because the average SBP in their trials were within the accepted range. Similarly, individual participants with an SBP within our accepted range were missed because they were included in trials with an average SBP outside our accepted range. Notably, this problem is not unique to this review, but applies to most meta-analyses in the field, including those comparing different blood pressure targets cited by guidelines. [8,36,37] Overcoming this would require individual-patient data, unfortunately not available to date. Secondly, the aggregated nature of our data also affects categorization of trials as primary or secondary preventive. In trials categorized as primary preventive, 17 % of participants had CAD, whereas in secondary preventive trials the corresponding number was 95 %. This represents reasonable separation between groups, although this aspect could also be explored further in individual-patient data meta-analyses. Thirdly, additional possible effect modifiers like age, sex, and other comorbidities would also require individual-patient data and were therefore not assessed. Fourthly, SBP was only moderately reduced in the trials included in our analyses; less so compared to previous meta-analyses including target-driven trials. Although a less pronounced effect on clinical outcomes would be expected, the observed SBP difference of 3.4 mm Hg during > 200 000 person-years of follow-up should have resulted in at least a tendency towards primary preventive benefit if such were present. Instead confidence intervals were fairly

narrow around the null effect. We cannot exclude that larger SBP reductions with more ambitious treatment would have resulted in clinical benefit, such as in the SPRINT trial, although based on our findings it seems unlikely. Fifthly, all but two of the included trials assessed the effect of renin-angiotensin-aldosterone system (RAAS) inhibitors. Whereas the generalizability of our findings to other drugs therefore could be questioned, previous meta-analyses have found no clinically meaningful difference between RAAS inhibitors and other first-line agents for hypertension control.

The arguments for lowering SBP treatment goals differ slightly between the ACC/AHA guidelines compared to the ESH/ESC guidelines.[5,6] Common to both sets of guidelines is that they put emphasis on the results of systematic reviews and meta-analysis. Whereas the ACC/AHA performed their own systematic review of trials comparing different targets,[8] the ESH/ESC refers mainly to two previously published papers combining results from target-trials and placebo-controlled trials.[36,37]

The main strength of this review, compared to the systematic reviews underlying the ACC/AHA and the ESH/ESC guidelines, is that it is limited to randomized double-blind placebo-controlled trials, protecting it against performance bias. Although the magnitude of this potential problem is unknown, target-driven trials may be susceptible to performance bias due to their non-blinded nature.[9] Possible indicators of such bias might be 20-30 % more unscheduled visits in the intensive treatment group, and a large non-cardiovascular component of the all-cause mortality reduction, seen in SPRINT.[7] Meta-analyses restricted to target-trials, such as the one by the ACC/AHA[8], may be especially susceptible to these kinds of biases, whereas the risk is probably lower in meta-analyses combing target-trials and placebo-controlled trials, such as those

underlying the ESH/ESC recommendations.[36,37] Notwithstanding, the different findings in our analysis compared to the ACC/AHA analysis should raise the question if performance bias does play a role in target-trials of antihypertensive treatment, exaggerating treatment effect estimates.

Another important difference between this analysis and the ones underlying the ACC/AHA and ESH/ESC guidelines is that we analyze primary preventive studies and secondary preventive studies separately. This is important because the evidence for BP lowering in the 130-140 mm Hg interval comes to a large extent from trials in people with established coronary artery disease (CAD). Before primary and secondary preventive trials are combined one has to ask if it is reasonable to extrapolate findings from CAD patients to healthy individuals. To answer this, it is important to consider possible mechanistic differences in these populations. In primary prevention, development of atherosclerosis is a sine qua non for succeeding cardiovascular events, and hence the effect of BP lowering treatment on the early stages of atherosclerosis becomes most important. In people with established CAD, on the other hand, angina and heart failure symptoms are closely related to myocardial oxygen balance, depending to a large extent on cardiac afterload which is proportional to systolic blood pressure.[38] Also, systolic blood pressure has been associated with changes in atheroma size, indicating that higher blood pressure may increase the risk of plaque rupture.[39] Therefore, it is not beyond reasonable doubt that BP lowering might work through different mechanisms depending on CAD status; in this situation, lumping trials with and without CAD patients should be avoided. The analyses presented here provide statistical support to the pathophysiologically based decision to separate patient categories. Indeed, it shows that

the observed benefit in previous analyses depends on inclusion of secondary preventive studies.

Lastly, the systematic reviews referred to as supportive of lower treatment targets in the ESH/ESC guidelines used meta-analyses standardized to systolic BP reductions of 10 mm Hg.[36,37] This might seem reasonable at first, but affects the results in ways that might not be clear to most readers.[16] Firstly, standardization amplifies treatment effects by about 50 %, because SBP reduction in the included trials was on average 6-8 mm Hg whereas results are standardized to 10 mm Hg. Secondly, standardization assumes that there is a linear association between blood pressure reduction and cardiovascular outcomes, which may not be the case in this blood pressure interval and may also be different for different outcomes. If indeed the association between BP reduction and cardiovascular event reduction were linear, one would expect decreased heterogeneity with standardization. Our previous results indicate that standardization increases heterogeneity and makes analyses highly sensitive to choice of statistical methods.[16] This is probably due to amplification of differences not related to BP lowering, paradoxically making standardized results less blood pressure-dependent. Thirdly, standardization of standard errors, which was applied in one of the referred meta-analyses, disrupts the association between number of events within trials and weight given to trials in meta-analyses.[16,36] For example, the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial, were given 7.3 % weight the all-cause mortality analysis, despite contributing with less than 0.3 % of participants.[36] Simply put, standardization makes results less representative of the underlying data.

Although arguments can be made for including target-trials, lumping different populations and using standardization, all these approaches build on assumptions that the current analysis does not make. If treatment benefit hinges on these assumptions, results are simply not robust enough to change guidelines for hundreds of millions of people worldwide. Meta-analyses using non-standardized methods have consistently found that the effects of antihypertensive treatment are attenuated at lower BP levels.[14,40-42] In a recent paper, we found 22 % reduced risk of MACE if baseline SBP was > 160 mm Hg, 12 % reduced risk in the 140-159 mm Hg SBP range, whereas in trials with baseline SBP below 140 mm Hg treatment effect was neutral for all efficacy outcomes. These results are well in line with the third Heart Outcomes Prevention Evaluation (HOPE-3) study, where 12 705 participants with average baseline BP 138/82 mm Hg were randomized to candesartan/hydrochlorothiazide combination therapy or matching placebo.[25] In fact, HOPE-3 is the only mega-trial aiming to assess the effect of antihypertensive treatment against double-blind placebo in mostly treatment naïve normotensive primary preventive patients. Neither the primary combined endpoints nor individual cardiovascular outcomes were reduced by treatment. However, there was a significant interaction between baseline SBP and treatment effect on MACE, with treatment benefit in the highest SBP tertile but a tendency towards harm in the lowest SBP tertile.

Treatment decisions should always be based on consideration of both benefit and harm. In situations where interventions are unlikely to be harmful, one may consider treatment despite weak or conflicting evidence. Unfortunately, randomized clinical trials, and systematic reviews of such trials, show incriminating signs of harm for antihypertensive treatment at BP levels now recommended in guidelines. In people with

diabetes mellitus, we have previously shown that BP-lowering treatment at SBP levels < 140 mm Hg is associated with 15 % increased risk of cardiovascular death.[40] Further down the ladder of seriousness and irreversibility comes an increased risk of chronic kidney disease,[43] acute kidney injury,[44] as well as hypotension-related adverse events and adverse events leading to treatment discontinuation presented here.

In summary, randomized double-blind placebo-controlled trials do not support primary preventive BP-lowering in the 130-140 mm Hg SBP range. Such treatment does not affect all-cause mortality or incident cardiovascular disease, but increases the risk of adverse events. In people with previous CAD, treatment may reduce the risk of all-cause mortality and MACE, at the cost of more pronounced risk increase for adverse events. In CAD patients, therefore, benefits should be balanced against potential harms for individual patients.

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Table 1. Study characteristics

Acronym (year)	Participants (n, age, sex)	Co-morbidity	Intervention/ Control	Baseline SBP/DBP (mm Hg)	SBP/DBP difference (mm Hg)
ACTION (2004)	7665 63 years 21 % female	100 % CAD 14 % DM	Nifedipine 60 mg vs. placebo	137.5/ 79.8	5.7/ 3.0
ACTIVE I (2011)	9016 70 years 29 % female	36 % CAD 20 % DM 100 % AF	Irbesartan 300 mg vs. placebo	138.3/ 82.4	2.9/ 1.9
ALTITUDE (2012)	8561 64 years 32 % female	26 % CAD 100 % DM 98 % CKD	Aliskiren 300 mg vs. placebo	137.3/ 74.2	1.3/ 0.6
BCAPS (2001)	793 62 years 55 % female	4 % CAD 3 % DM All had carotid plaques	Metoprolol CR/XL 25 mg vs. placebo	138.9/ 84.7	1.3/ -
DREAM (2006)	5269 55 years 59 % female	0 % CAD 0 % DM All had IGT/IFG	Ramipril 15 mg vs. placebo	136/ 83.4	4.3/ 2.7
EUROPA (2003)	12 218 60 years 15 % female	100 % CAD 12 % DM	Perindopril 8 mg vs. placebo	137/ 82	5/ 2
HOPE (2000)	9297 66 years 27 % female	81 % CAD 38 % DM	Ramipril 10 mg vs. placebo	139/ 79	3/ 2*
HOPE-3 (2016)	12 705 66 years 46 % female	0 % CAD 6 % DM	Candesartan/ HCTZ 16/12.5 mg vs. placebo	138.1/ 81.9	6/ 3
Lewis (1993)	409 35 years 47 % female	100 % DM (type 1) All with nephropathy	Captopril 75 mg vs. placebo	138.5/ 85.5	1.5/ 2.5
NAVIGATOR (2010)	9306 64 years 51 % female	24 % CAD 0 % DM 100 % IGT	Valsartan 160 mg vs. placebo	139.7/ 82.6	2.8/ 1.4
PART-2 (2000)	617 61 years 18 % female	68 % CAD (100 % CVD) 9 % DM	Ramipril 5-10 mg vs. placebo	133/ 79	5.5/ 4
PEACE (2004)	8290 64 years 18 % female	100 % CAD 17 % DM	Trandolapril 4 mg vs. placebo	133/ 78	3.0/ 1.2
PHARAO (2008)	1008 62 years 52 % female	6 % CAD 13 % DM	Ramipril 5 mg vs. placebo	134.4/ 83.6	2.8/ 0.9

PREVEND-IT (2004)	864 51 years 35 % female	3 % CAD 3 % DM	Fosinopril 20 mg vs. placebo	130/ 76	3/ 3
Ravid (1998)	194 55 years 51 % female	0 % CAD 100 % DM	Enalapril 10 mg vs. placebo	MAP 97	-/ -
ROADMAP (2011)	4447 58 years 54 % female	25 % CAD 100 % DM	Olmesartan 40 mg vs. placebo	136.5/ 80.5	3.1/ 1.9
SCAT (2000)	460 61 years 11 % female	100 % CAD 11 % DM	Enalapril 10 mg vs. placebo	130/ 77.5	5.2/ 3.3
VA-NEPHRON (2013)	1448 65 years 0.3 % female	23 % CAD 100 % DM with nephro-pathy	Losartan/ lisinopril 100/10-40 mg vs. losartan 100 mg	137.0/ 72.7	1.5/ 1.0

* A sub-study assessing ABPM found larger BP differences between groups during follow-up, indicating potentially underestimated BP differences in the main publication. SBP = systolic blood pressure. DBP = diastolic blood pressure. CAD = coronary artery disease. DM = diabetes mellitus. AF = atrial fibrillation. CKD = chronic kidney disease. IGT = impaired glucose tolerance. IFG = impaired fasting glucose. HCTZ = hydrochlorothiazide. MAP = mean arterial pressure.

Table 2. Secondary outcomes

		Primary prevention trials			Coronary artery disease trials		
		Trials/ participants/ events (n)	RR (95 % CI)	I^2 (%)	Trials/ participants/ events (n)	RR (95 % CI)	I^2 (%)
Efficacy outcomes	Cardiovascular mortality	8 / 49 685 / 2390	1.07 (0.95-1.21)	27.3	5 / 37 589 / 1802	0.86 (0.74-1.00)	55.7
	Myocardial infarction	8 / 46 682 / 1092	1.03 (0.91-1.15)	0.0	5 / 29 893 / 2367	0.83 (0.72-0.97)	60.0
	Stroke	9 / 47 546 / 1536	0.89 (0.73-1.09)	52.9	6 / 38 049 / 943	0.79 (0.66-0.94)	36.6
	Heart failure	6 / 44 881 / 1903	0.90 (0.81-1.00)	17.7	5 / 37 589 / 957	0.76 (0.67-0.86)	0.0
Safety outcomes	Hypotension-related AEs	6 / 44 058 / 5141	1.71 (1.32-2.22)	90.3	3 / 28 817 / 793	1.63 (1.01-2.63)	85.9
	Renal impairment	8 / 49 627 / 992	1.20 (0.93-1.55)	71.6	1 / 12 215 / 36	1.25 (0.65-2.41)	-

RR = relative risk. CI = confidence interval. AEs = adverse events

Figure legends

Figure 1 – Treatment effect on primary outcomes in primary prevention. CI = confidence interval.

Figure 2 – Treatment effect on primary outcomes in coronary artery disease trials. CI = confidence interval.

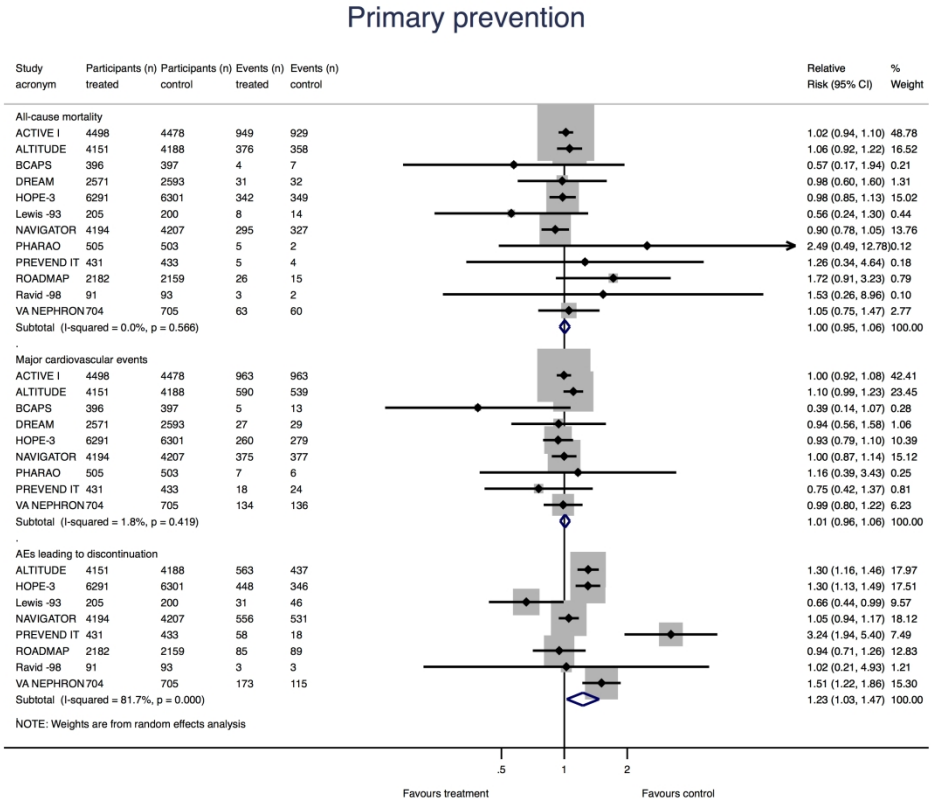

Figure 1 – Treatment effect on primary outcomes in primary prevention. CI = confidence interval.

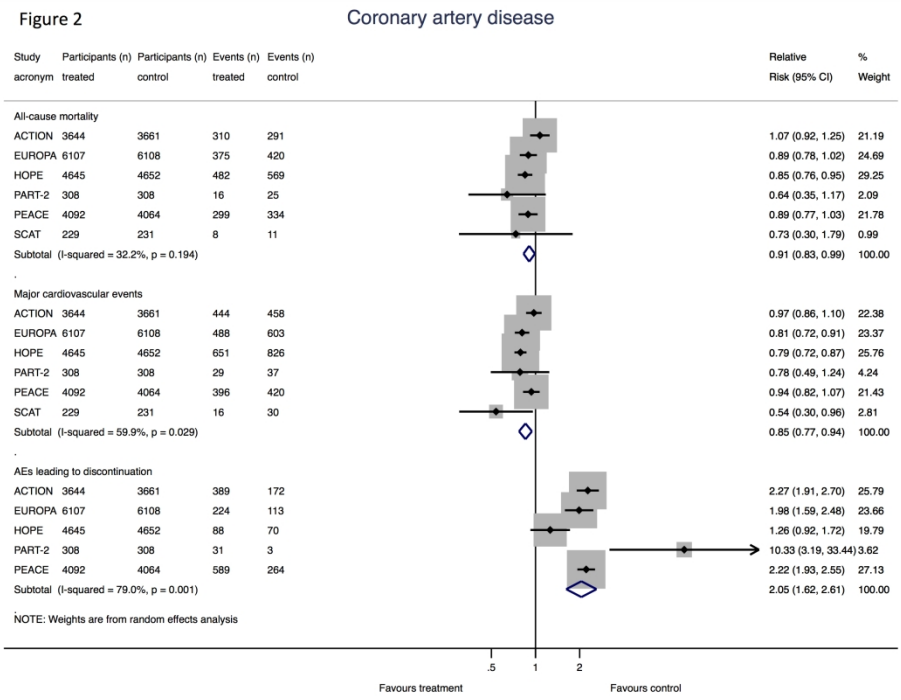

Figure 2 – Treatment effect on primary outcomes in coronary artery disease trials. CI = confidence interval.

ONLINE SUPPLEMENT

Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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eMethods - Search strategy for previous systematic review

The previous systematic review used a two-stage approach. First, we searched for systematic reviews of randomized controlled trials assessing antihypertensive treatment. All trials included in any previous systematic review were judged in full text against our eligibility criteria. We then performed an additional search for randomized controlled trials published after the latest previous search (with a few months overlap to account for time lag in indexing).

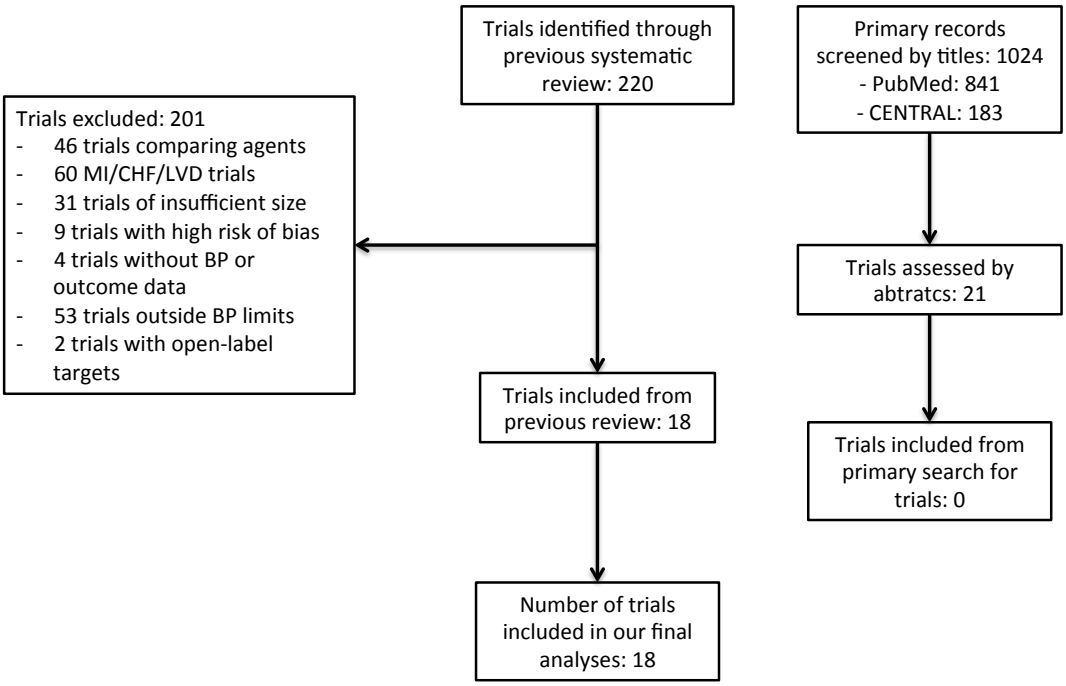
Search strategy systematic reviews
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke) in all databases, adding the filter for meta-analyses in PubMed.

The titles of the retrieved articles were browsed to identify reviews concerning the effect of BP lowering on death, cardiovascular events and renal disease. Reviews concerning treatment of other conditions, effects of specific agents, or the effect of BP lowering on other outcomes, were discarded. All randomized controlled trials included in any of the reviews deemed relevant were retrieved in full text and judged according to the above eligibility criteria.

Search strategy for randomized controlled trials
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke), adding ("2015/11/01"[Date – Publication] : "3000"[Date – Publication]) to the PubMed search and limiting the CENTRAL search to 2015-2017.

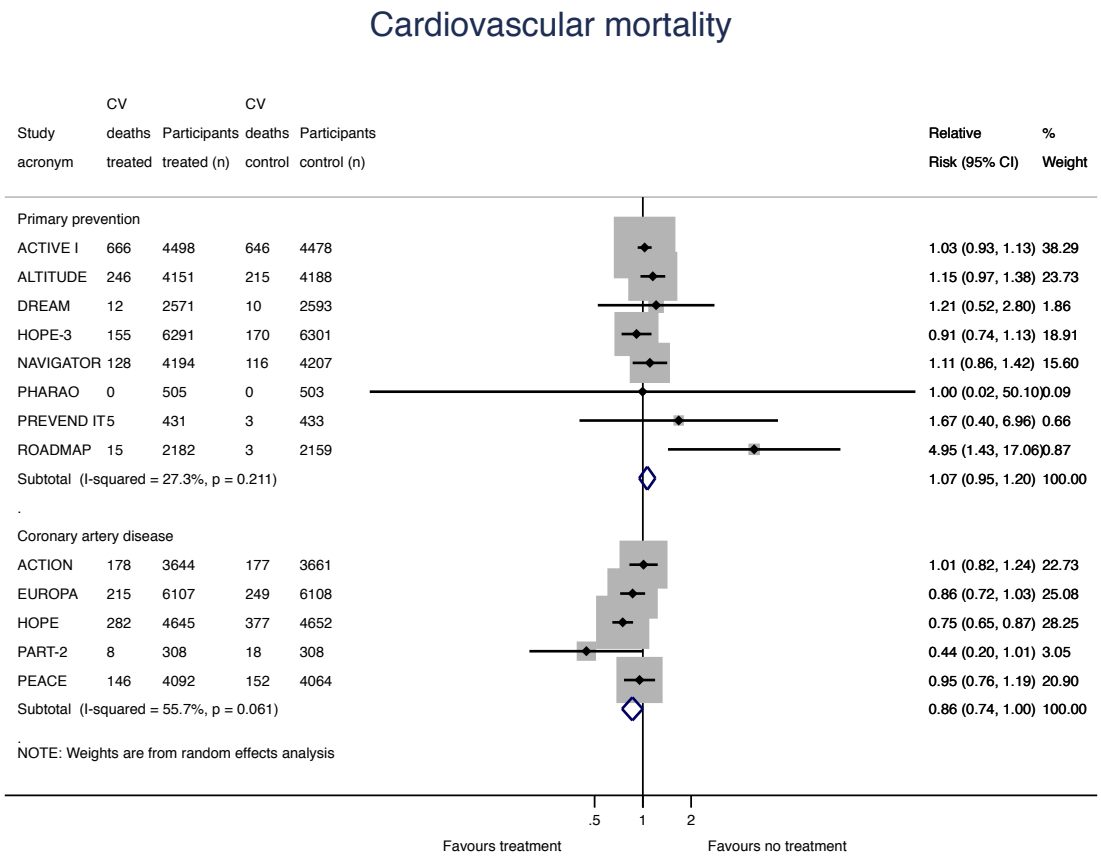
We also performed an alternative PubMed search, using the phrase (("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND ("2015/11/01"[Date - Publication] : "3000"[Date - Publication])) with RCT filter.

eFigure 1 - PRISMA flow chart



CENTRAL = Cochrane Central Register for Controlled Trials. MI = myocardial infarction. CHF = congestive heart failure. LVD = left ventricular dysfunction. BP = blood pressure.

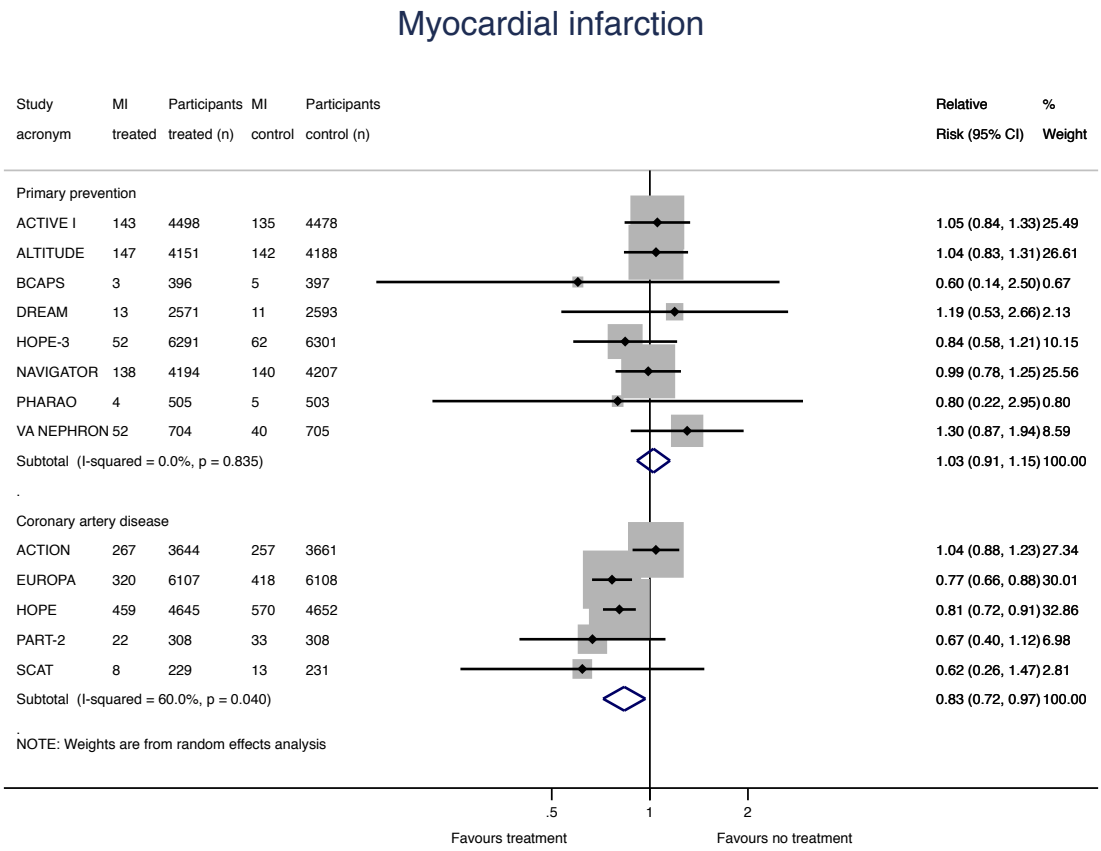
eFigure 2 – Forest plot for cardiovascular mortality



CV = cardiovascular.

Random-effects metaregression for interaction (p=0.047)

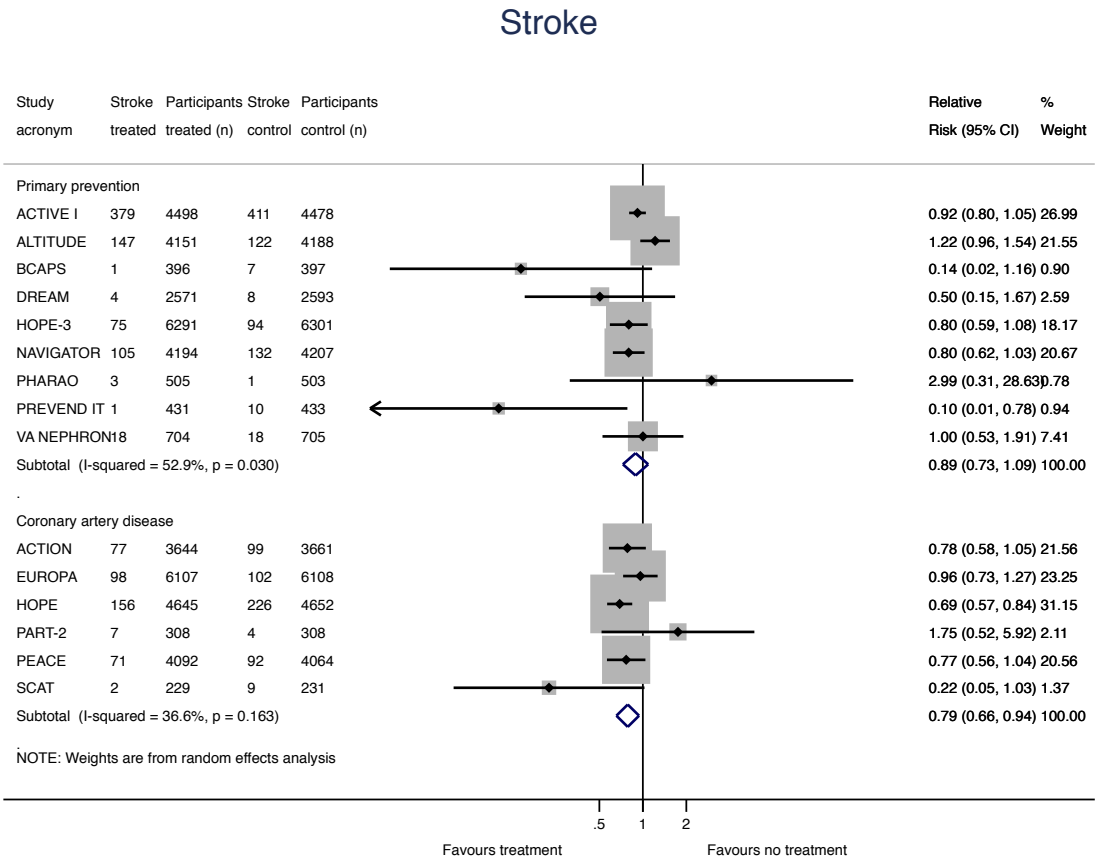
eFigure 3 – forest plot for myocardial infarction



MI = myocardial infarction.

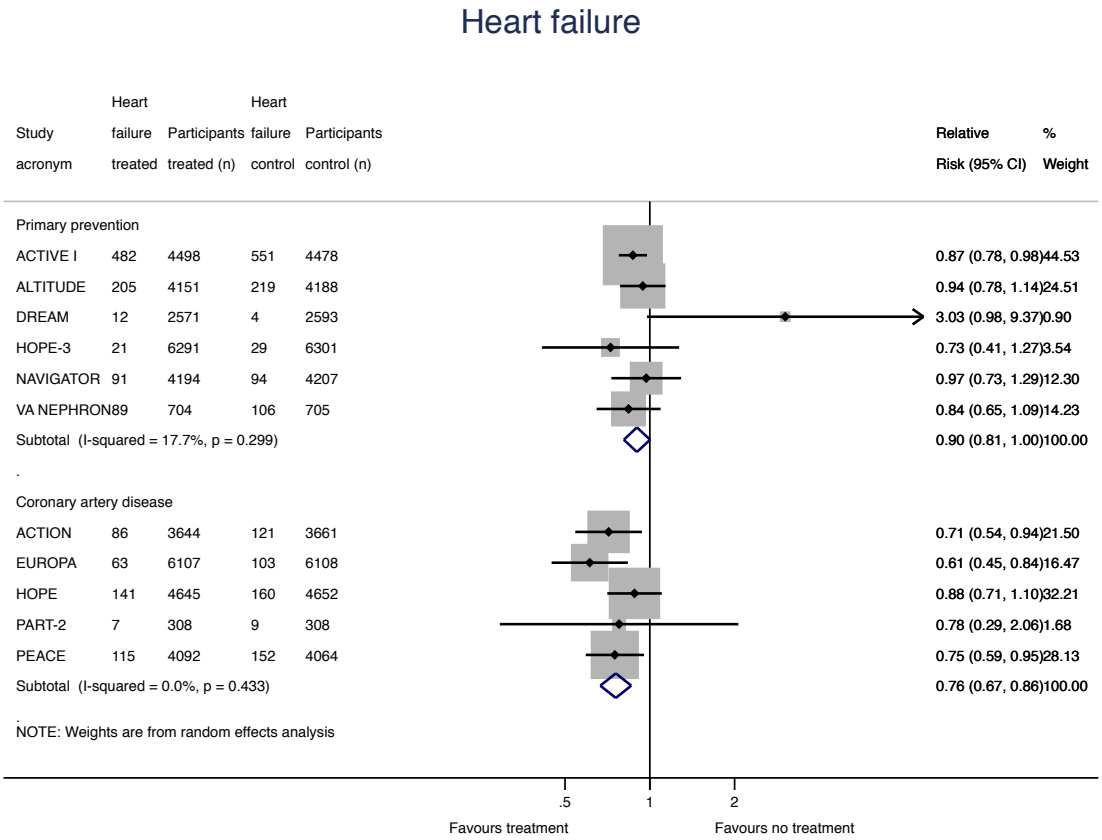
Random-effects metaregression for interaction (p=0.061)

eFigure 4 – forest plot for stroke



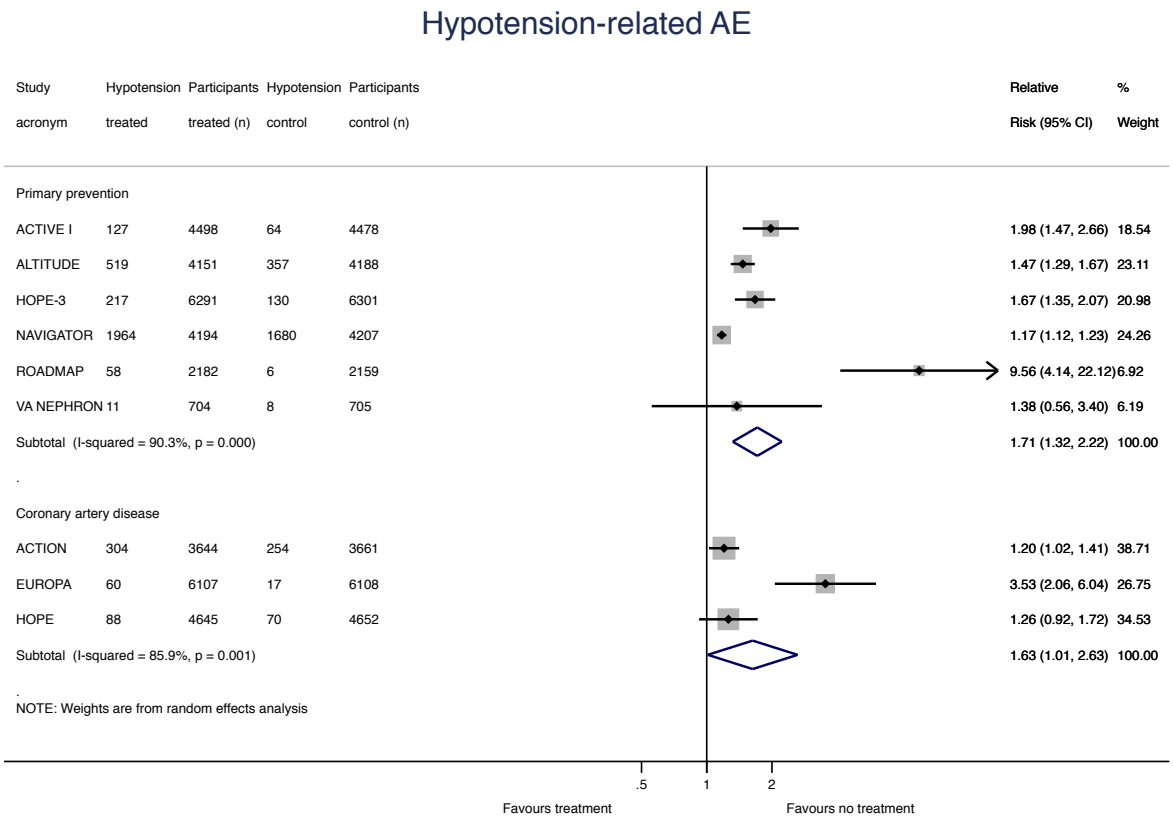
Random-effects metaregression for interaction (p=0.329)

eFigure 5 – forest plot for heart failure



Random-effects metaregression for interaction (p=0.072)

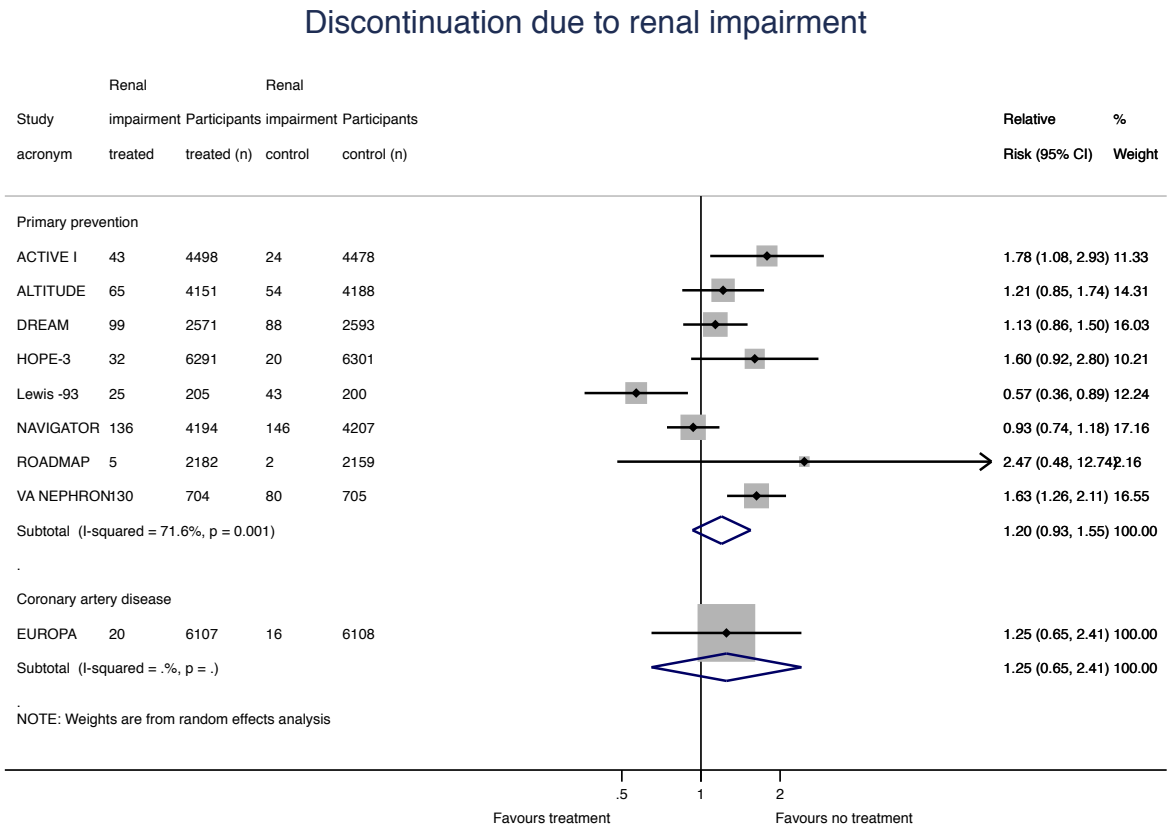
eFigure 6 – forest plot for hypotension-related AEs



AEs = adverse events

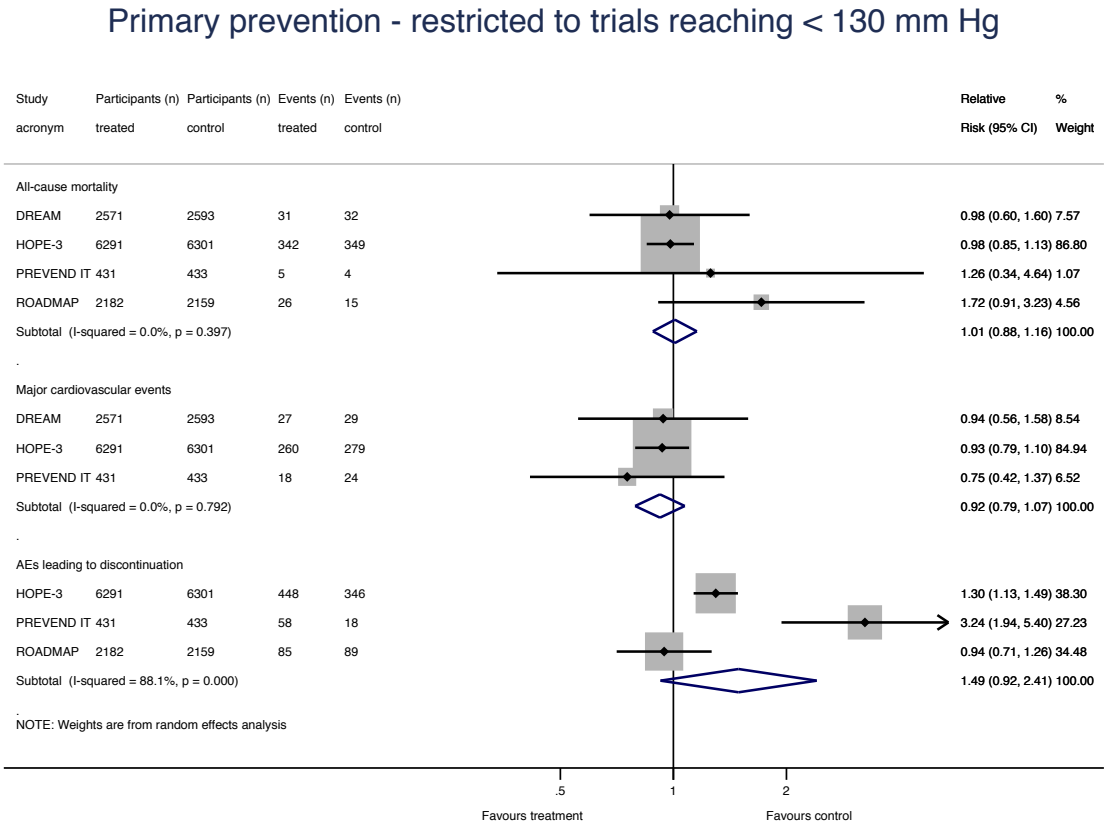
Random-effects metaregression for interaction (p=0.798)

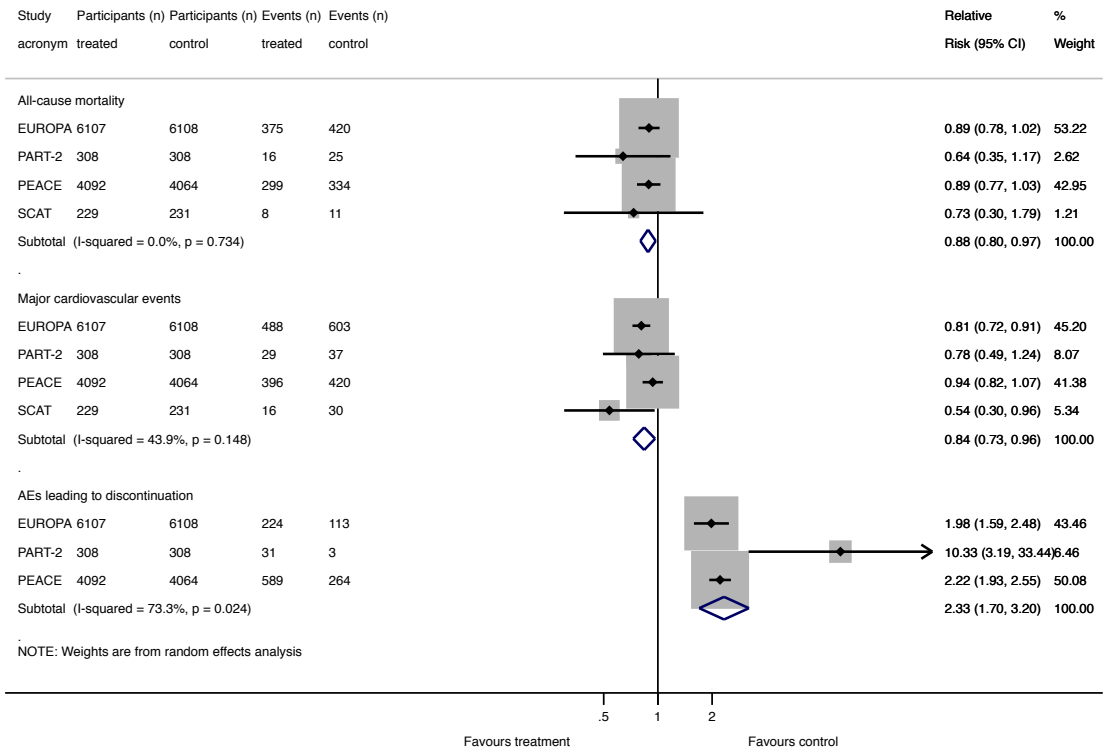
eFigure 7 – forest plot for renal impairment



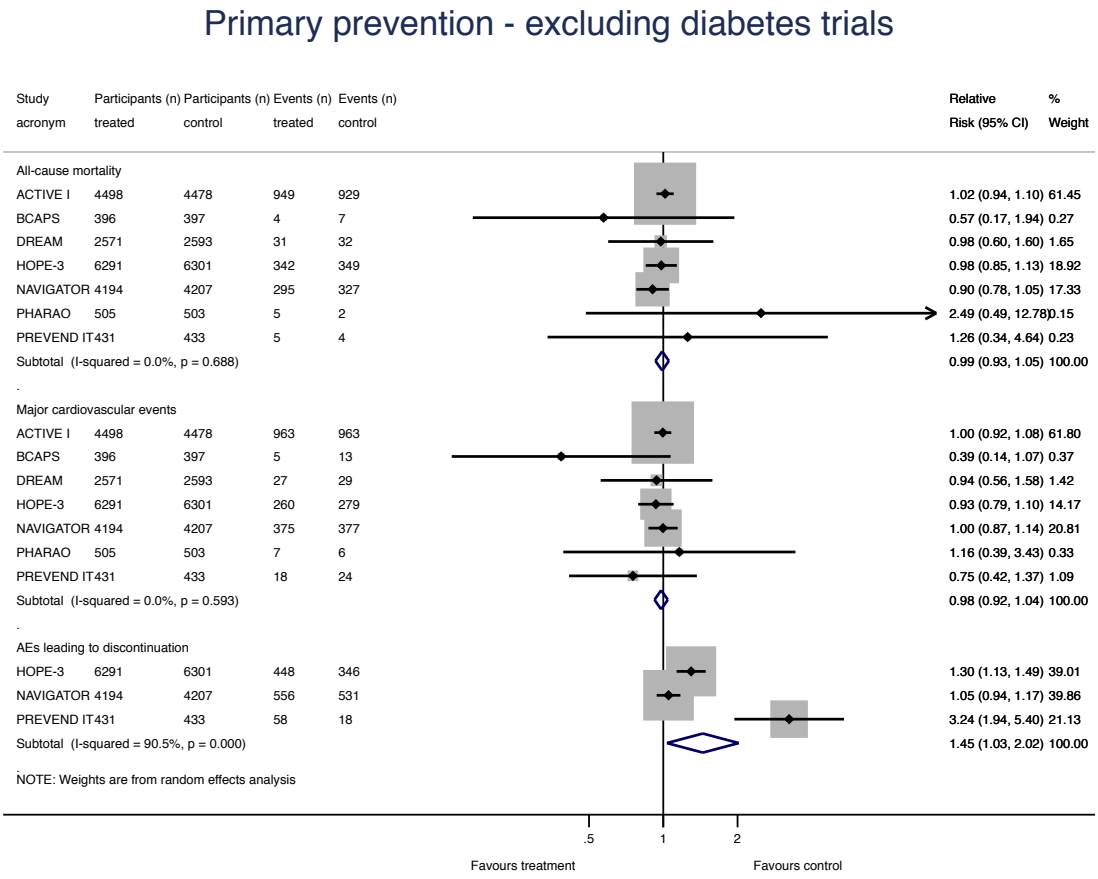
Random-effects metaregression for interaction (p=0.936)

eFigure 8 – Sensitivity analysis excluding trials not reaching < 130 mm Hg



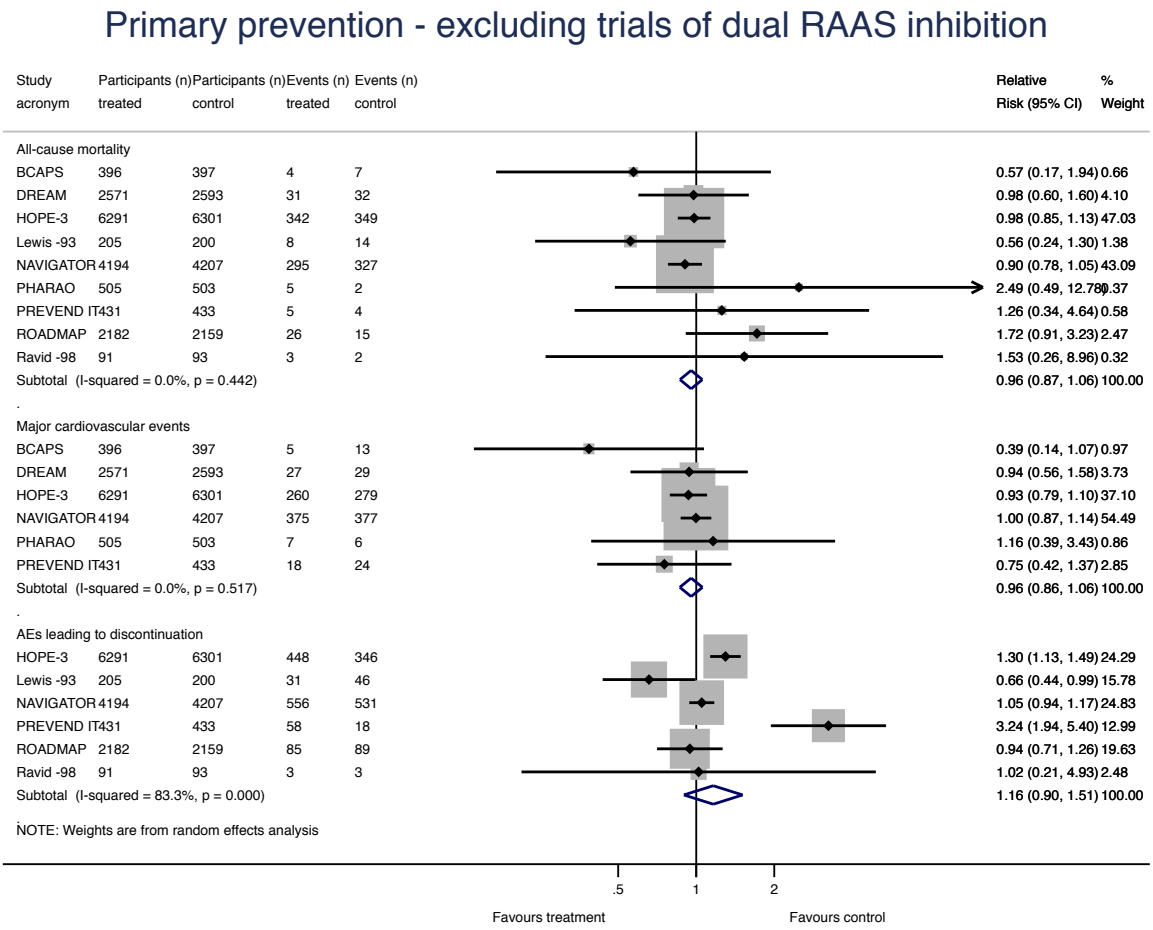


eFigure 9 – sensitivity analysis excluding trials in people with diabetes



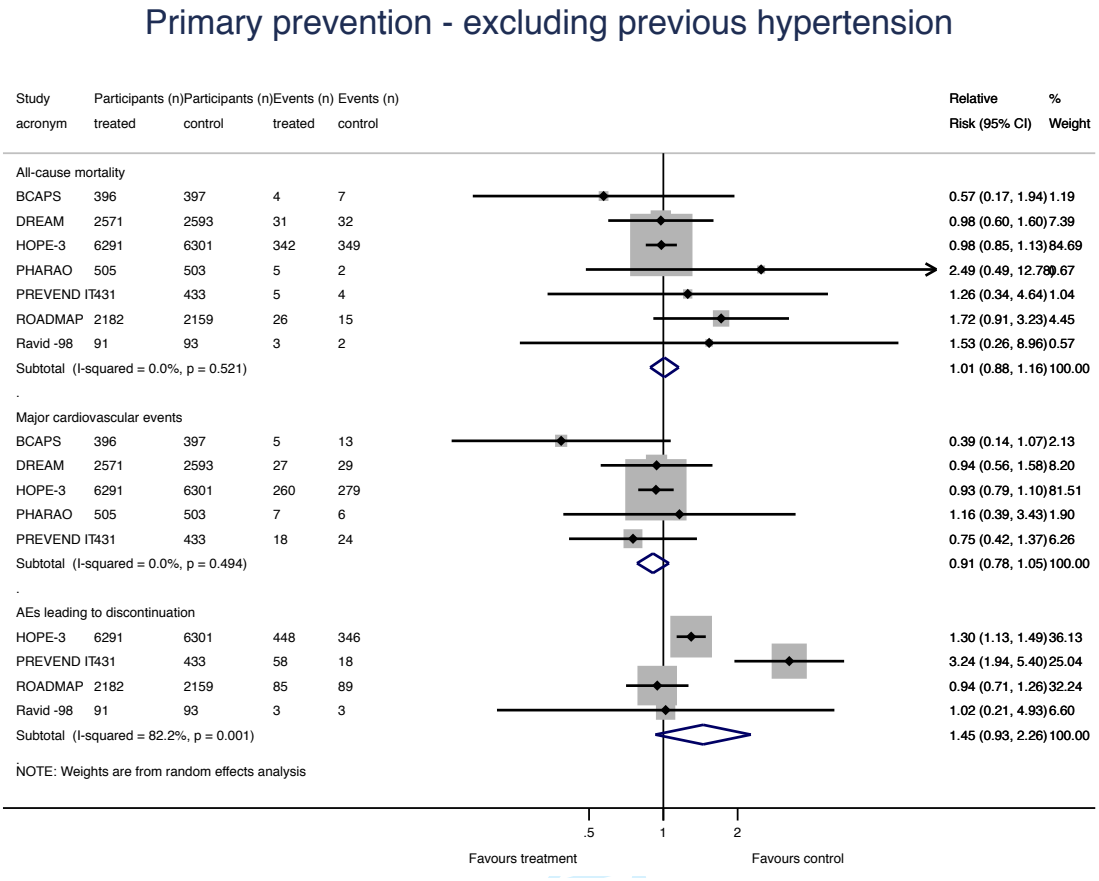
Note: None of CAD trials were primarily in people with diabetes. Hence, no sensitivity analysis was performed.

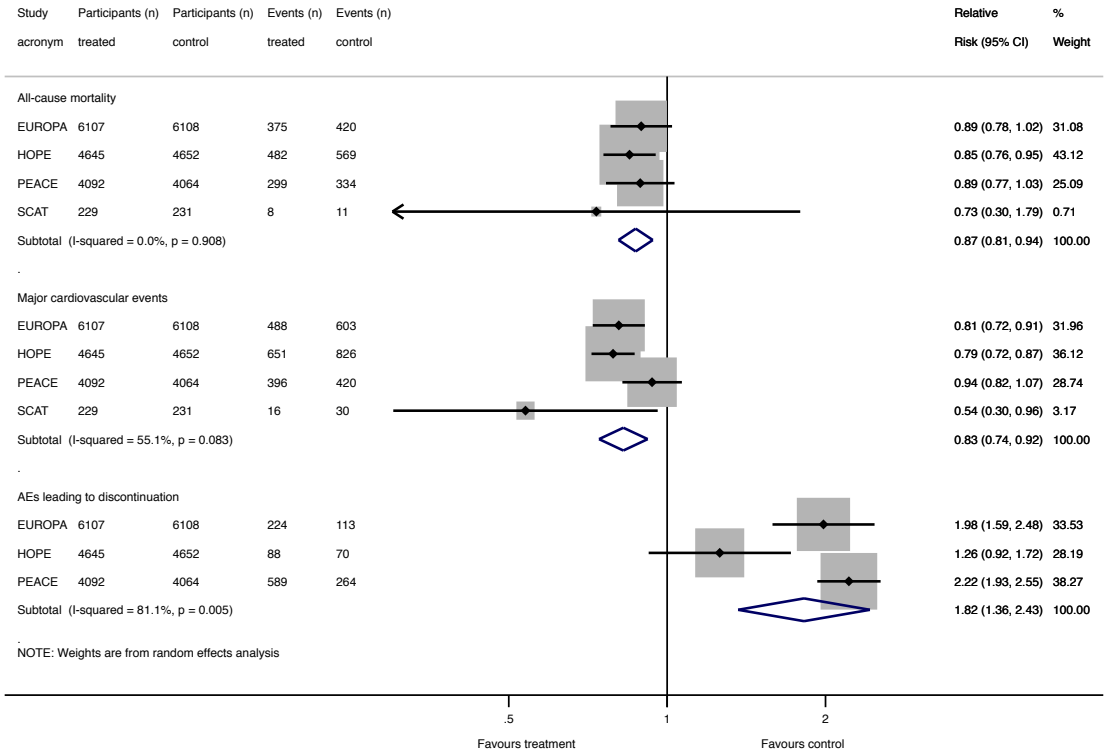
eFigure 10 – sensitivity analysis excluding trials of dual RAAS-inhibition



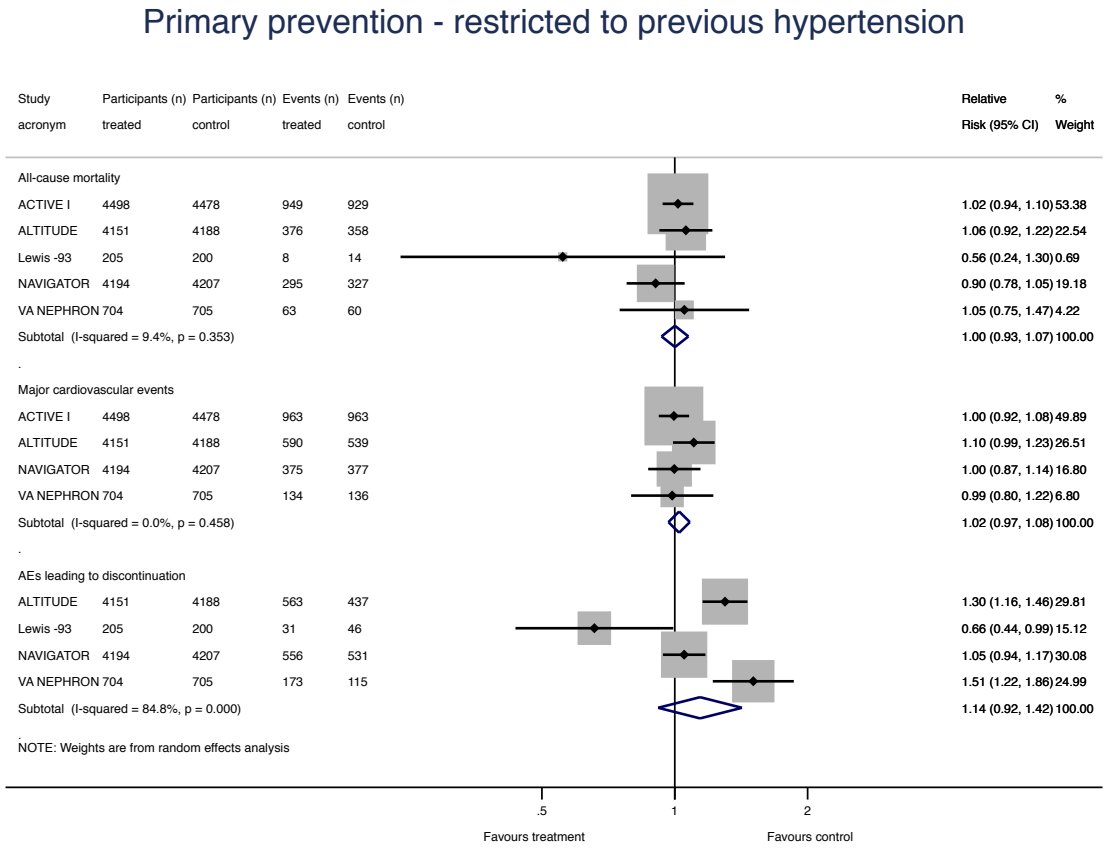
Note: None of CAD trials were testing dual RAAS inhibition. Hence, no sensitivity analysis was performed.

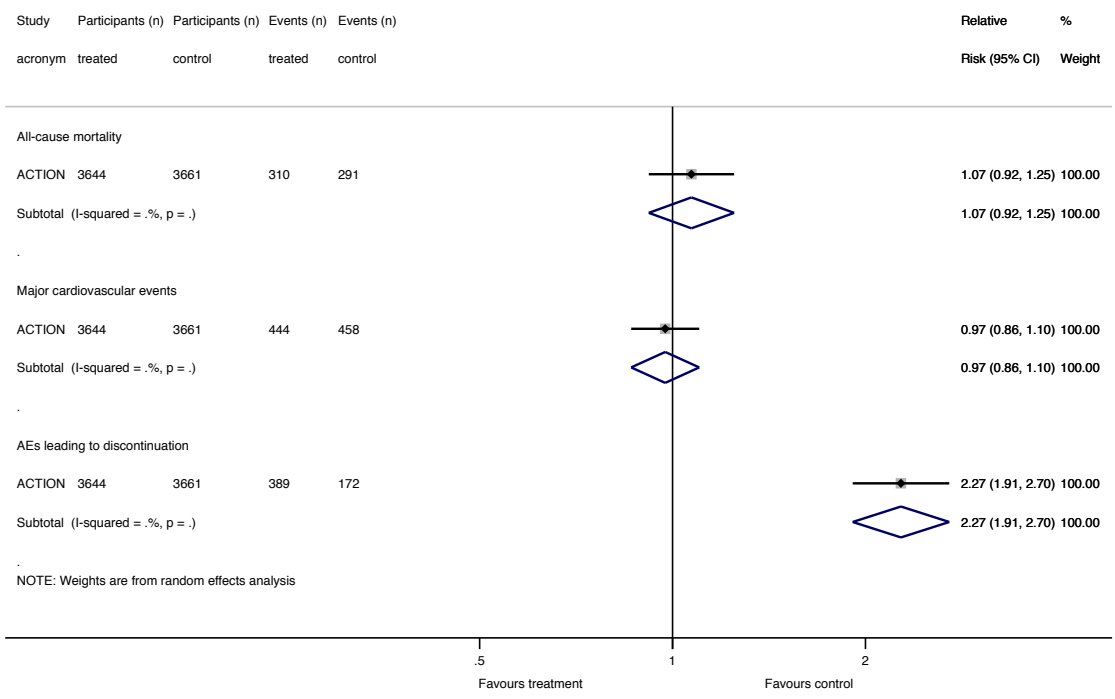
eFigure 11 – sensitivity analysis excluding trials in people with hypertension



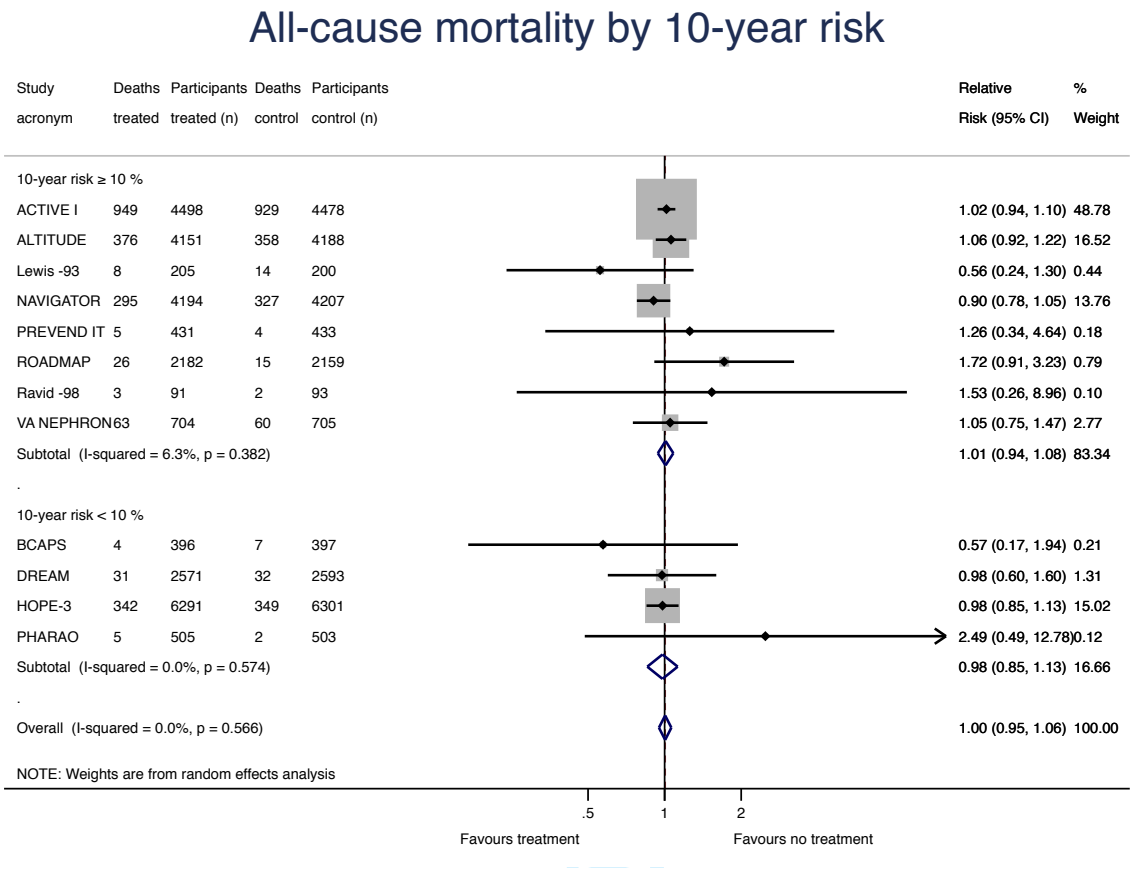


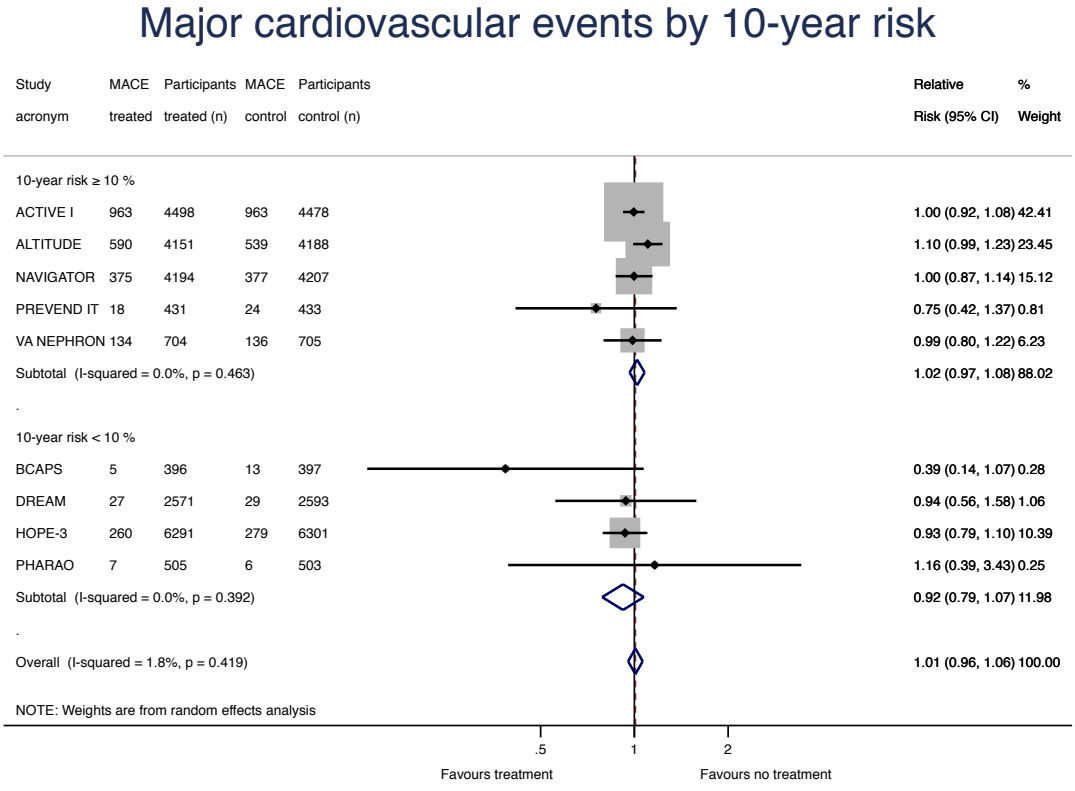
eFigure 12 – sensitivity analysis restricted to trials in people with hypertension

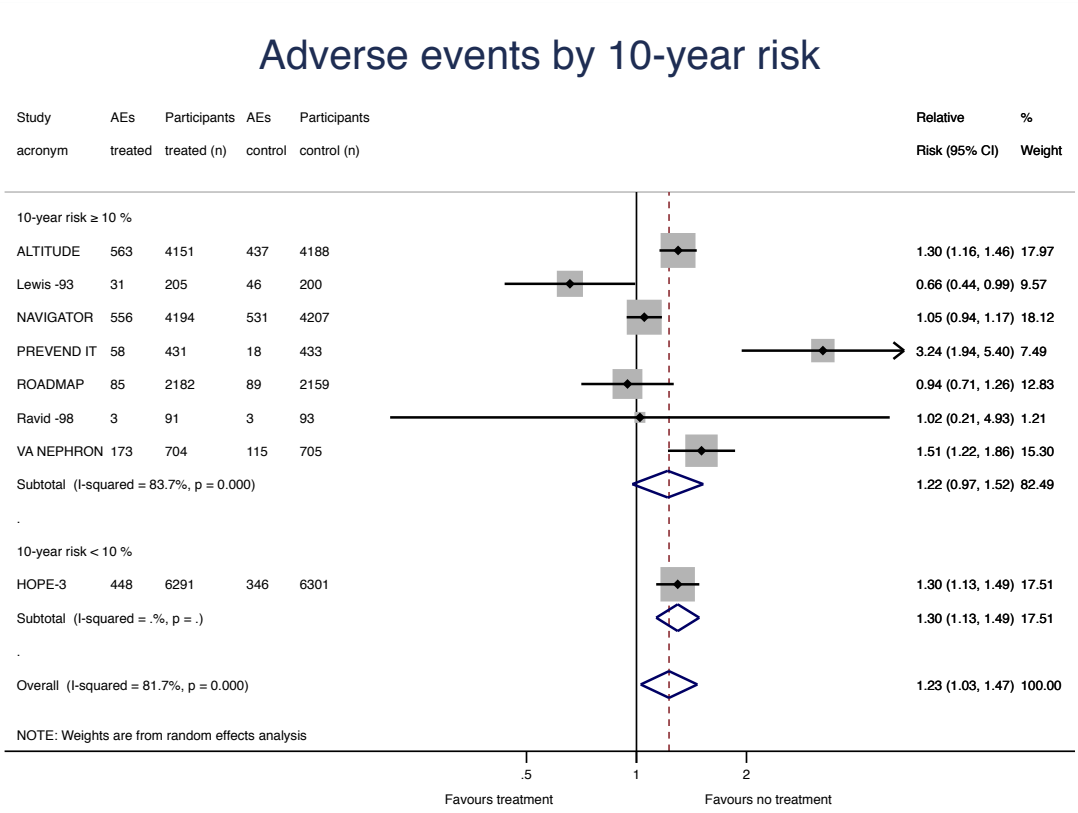




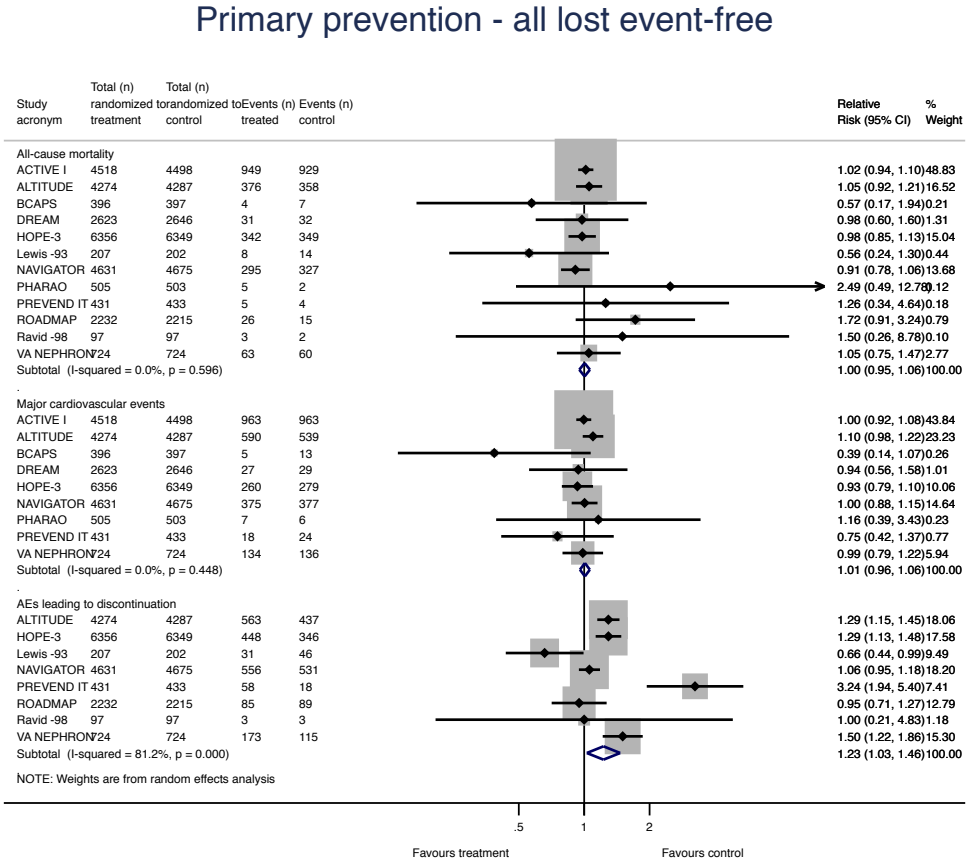
eFigure 13 – Primary preventive trials stratified by 10-year cardiovascular risk

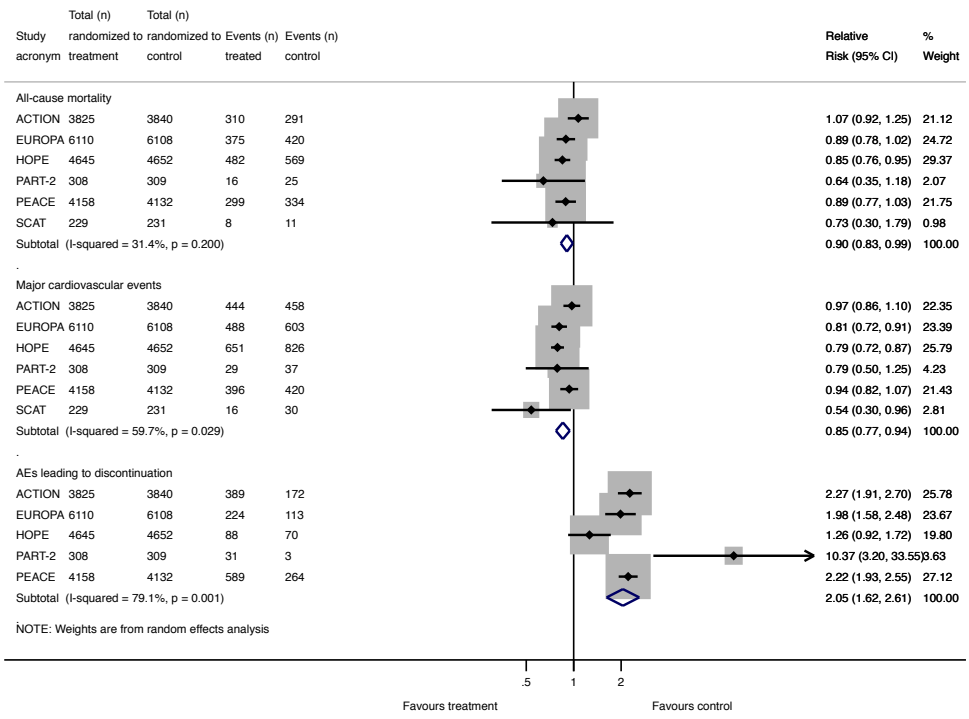




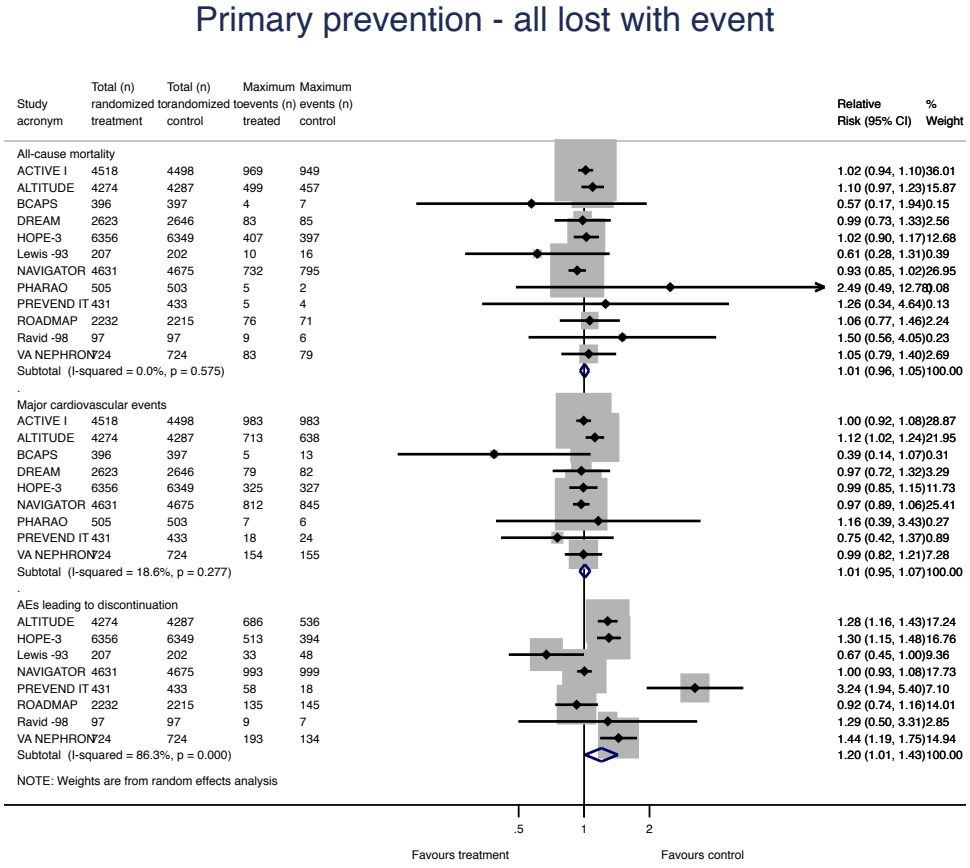

Adverse events by 10-year risk
Study acronym
AEs treated
Participants treated (n)
AEs control
Participants control (n)
Relative Risk (95% CI)
% Weight
10-year risk ≥ 10 %
ALTITUDE 563 4151 437 4188 1.30 (1.16, 1.46) 17.97
Lewis -93 31 205 46 200 0.66 (0.44, 0.99) 9.57
NAVIGATOR 556 4194 531 4207 1.05 (0.94, 1.17) 18.12
PREVEND IT 58 431 18 433 3.24 (1.94, 5.40) 7.49
ROADMAP 85 2182 89 2159 0.94 (0.71, 1.26) 12.83
Ravid -98 3 91 3 93 1.02 (0.21, 4.93) 1.21
VA NEPHRON 173 704 115 705 1.51 (1.22, 1.86) 15.30
Subtotal (I-squared = 83.7%, p = 0.000) 1.22 (0.97, 1.52) 82.49
10-year risk < 10 %
HOPE-3 448 6291 346 6301 1.30 (1.13, 1.49) 17.51
Subtotal (I-squared = .%, p = .) 1.30 (1.13, 1.49) 17.51
Overall (I-squared = 81.7%, p = 0.000) 1.23 (1.03, 1.47) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
Favours treatment
Favours no treatment

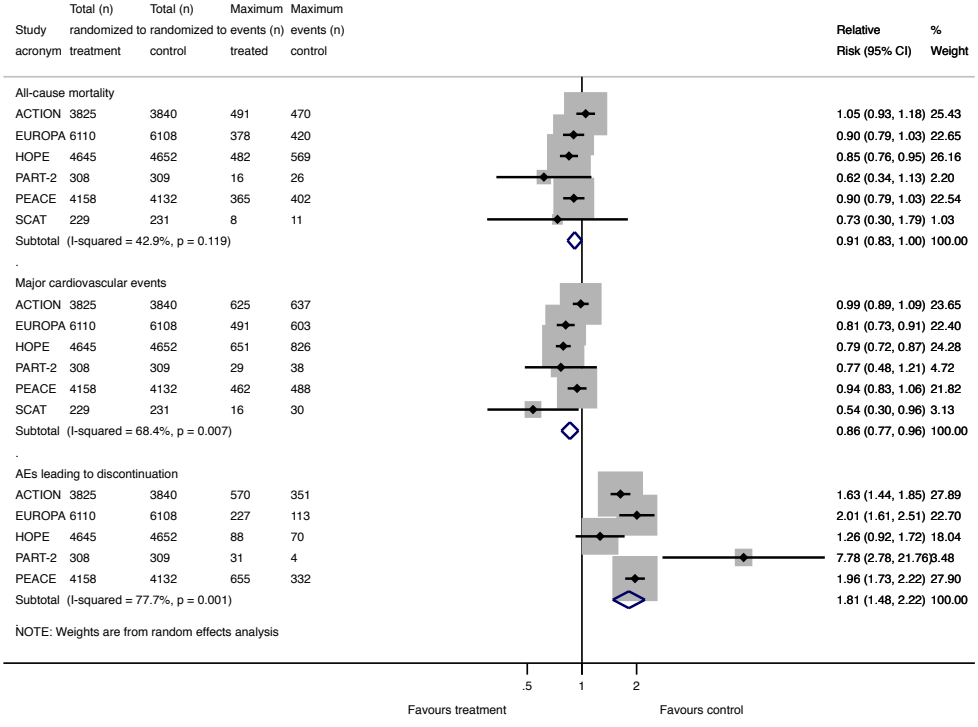
eFigure 14 - Lost to follow-up imputed as event-free



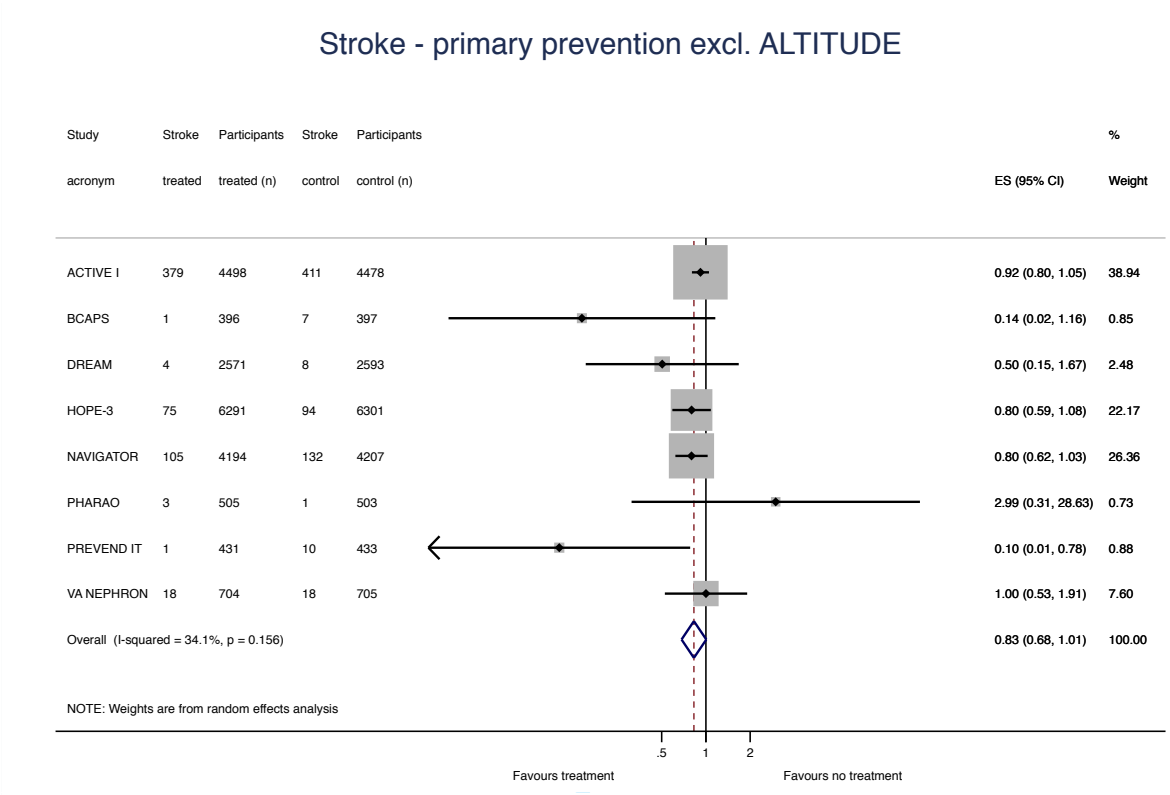


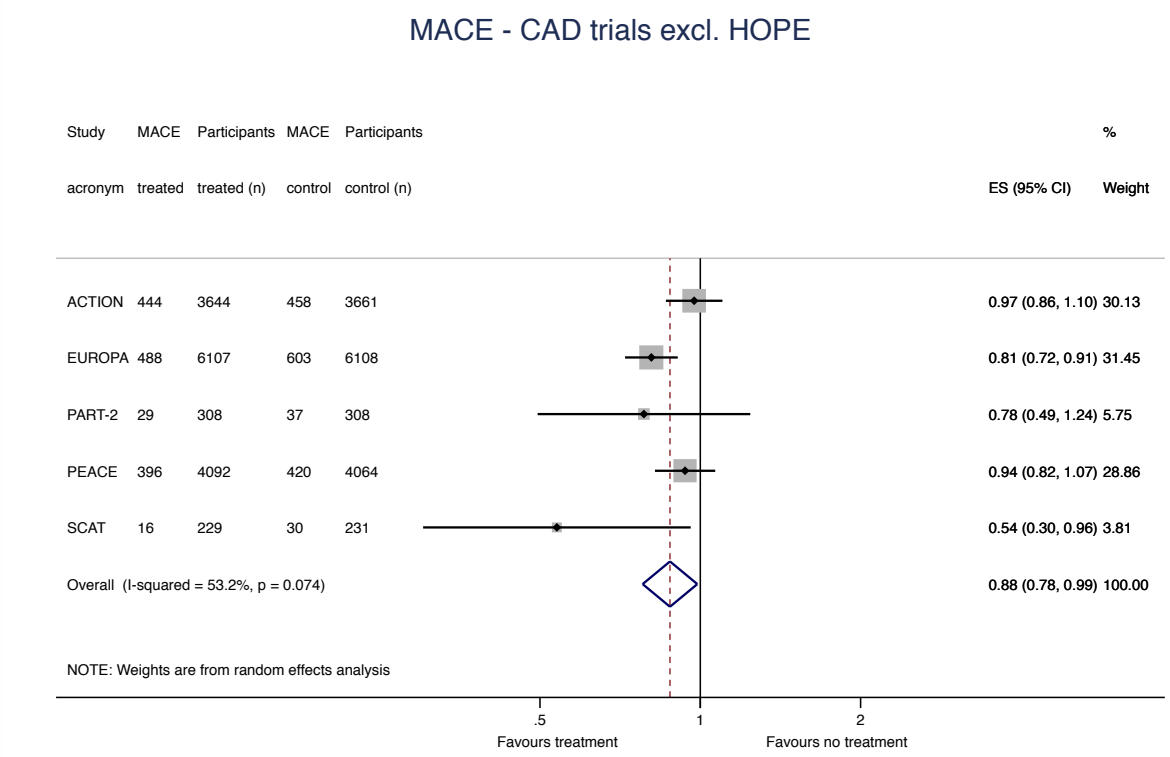
eFigure 15 - lost to follow-up imputed as having an event



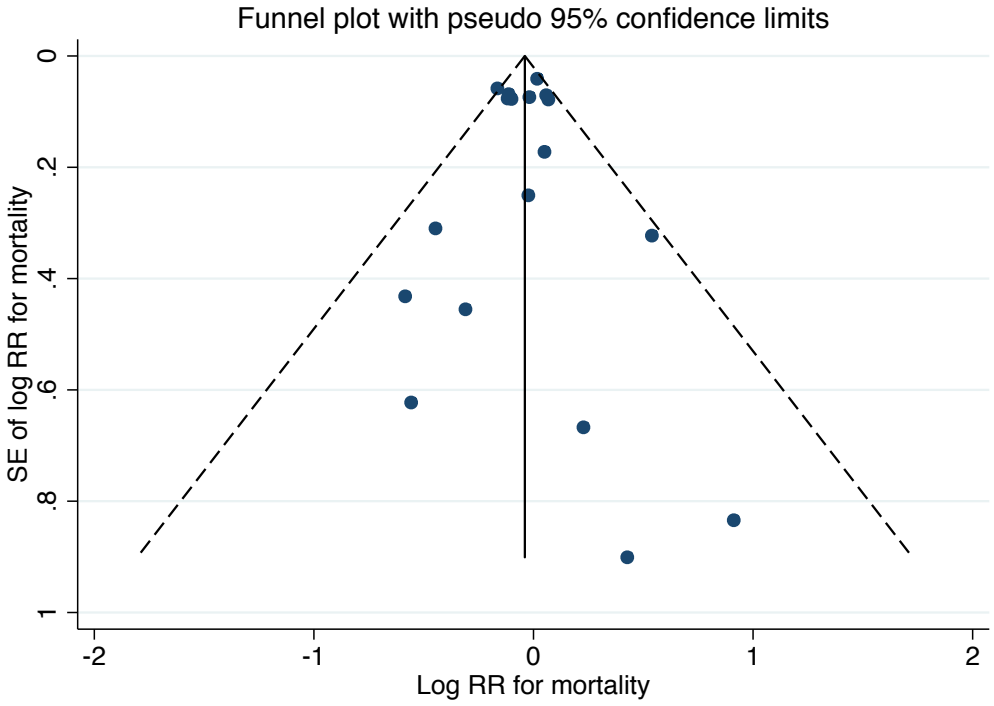


eFigure 16 - Ad hoc sensitivity analyses based on risk of bias assessment



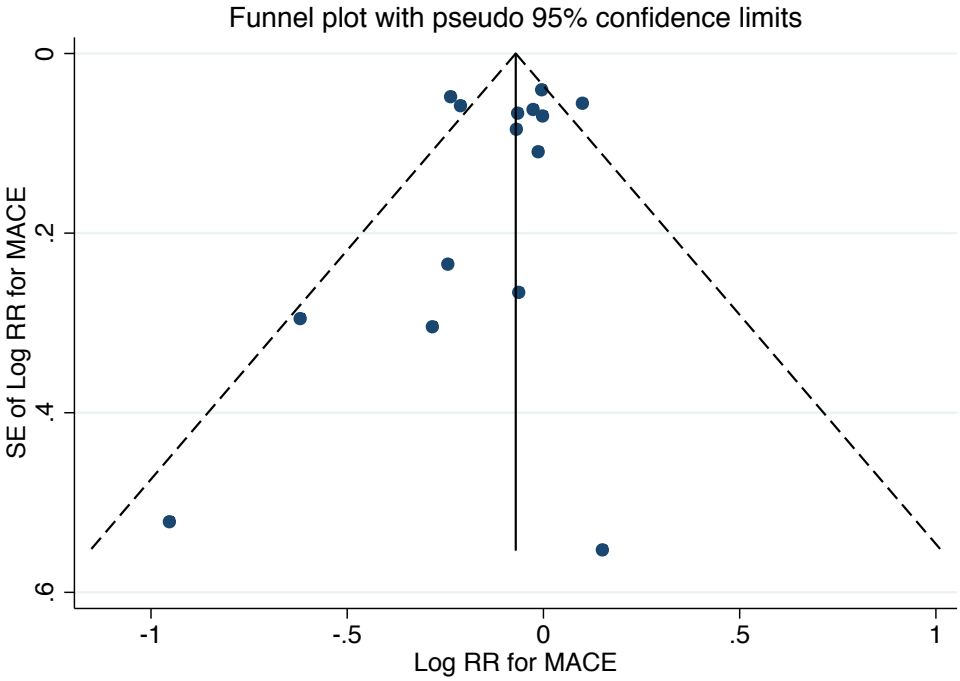


eFigure 17 – Funnel plot for all-cause mortality



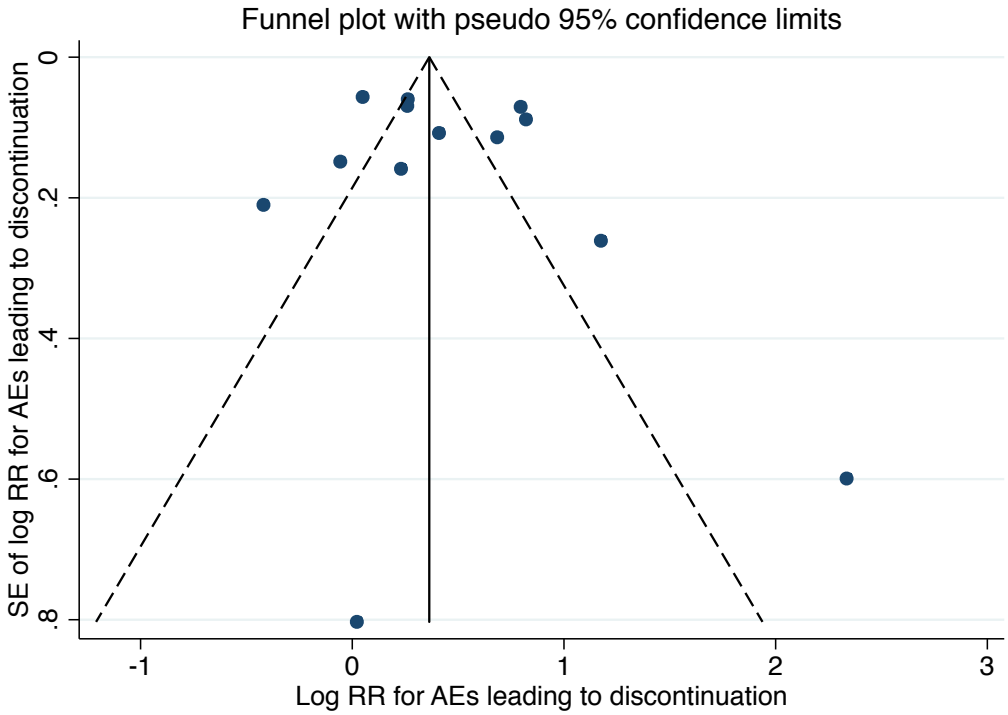
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.938

eFigure 18 – Funnel plot for major cardiovascular events



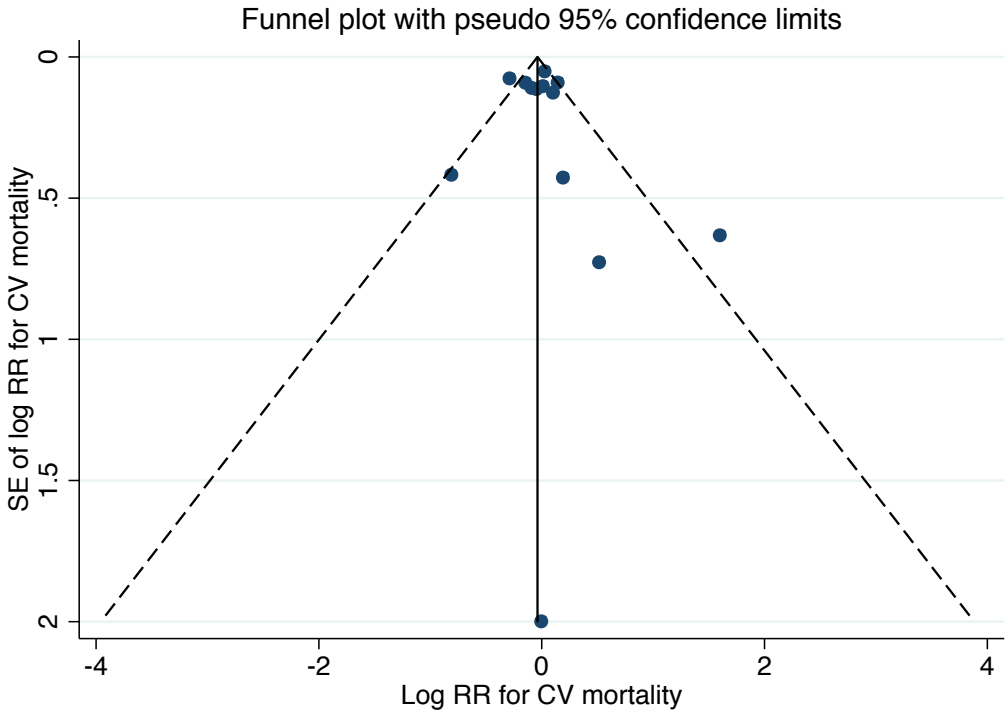
RR = relative risk. SE = standard error. MACE = major cardiovascular events.
Harbord's test for small-study effects p = 0.410

eFigure 19 – Funnel plot for adverse events leading to discontinuation



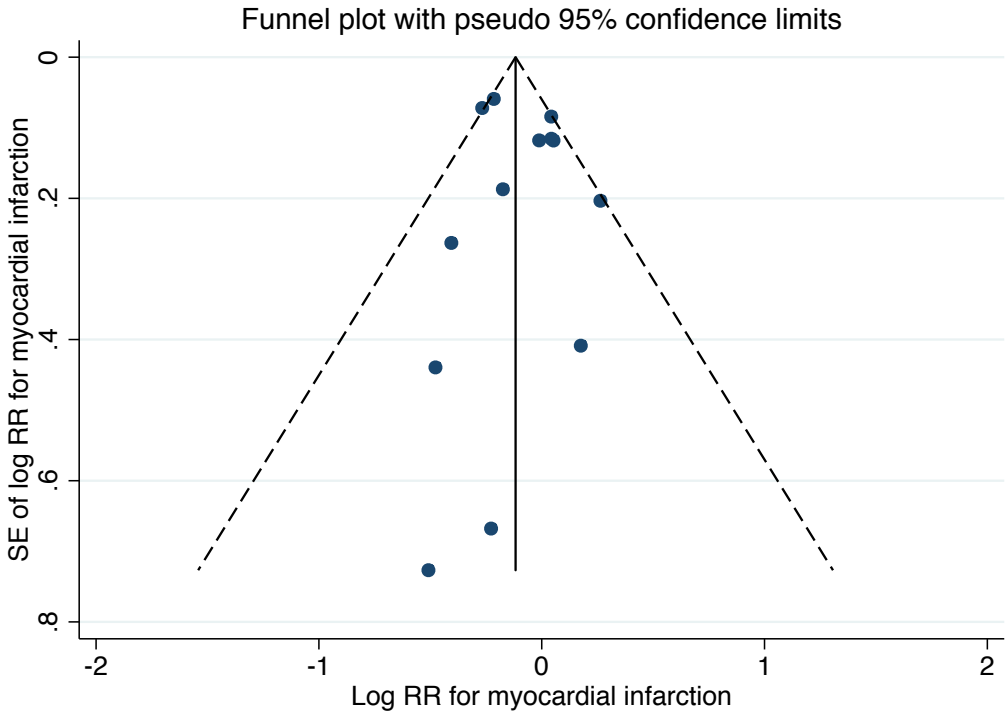
RR = relative risk. SE = standard error. AEs = adverse events.
Harbord's test for small-study effects p = 0.712

eFigure 20 – Funnel plot for cardiovascular mortality



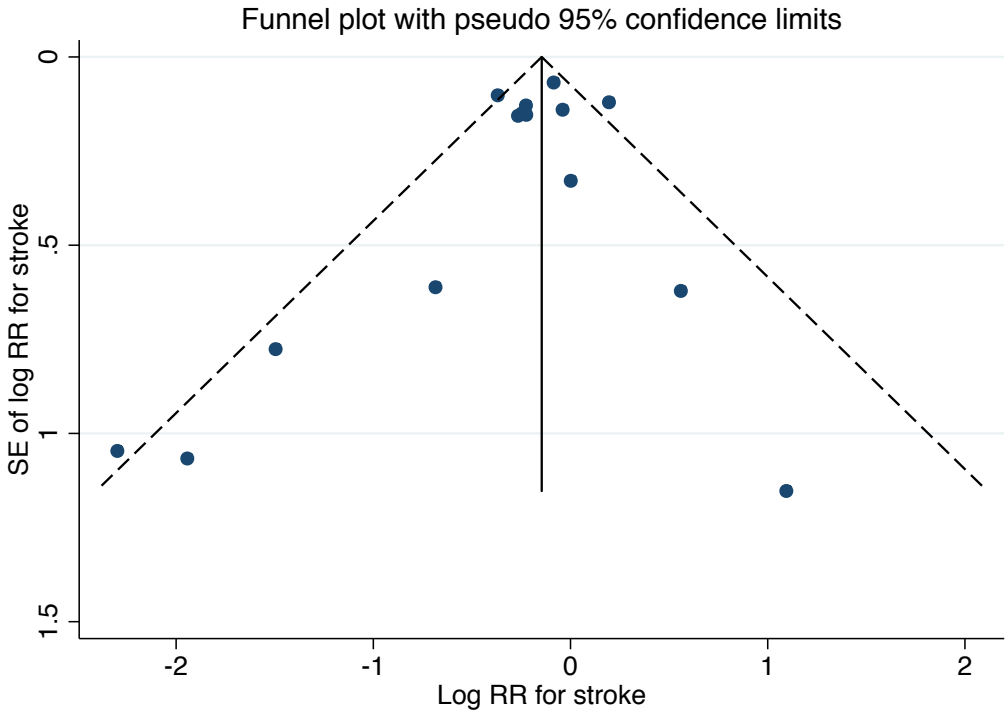
RR = relative risk. SE = standard error. CV = cardiovascular.
Harbord's test for small-study effects p = 0.507

eFigure 21 – Funnel plot for myocardial infarction



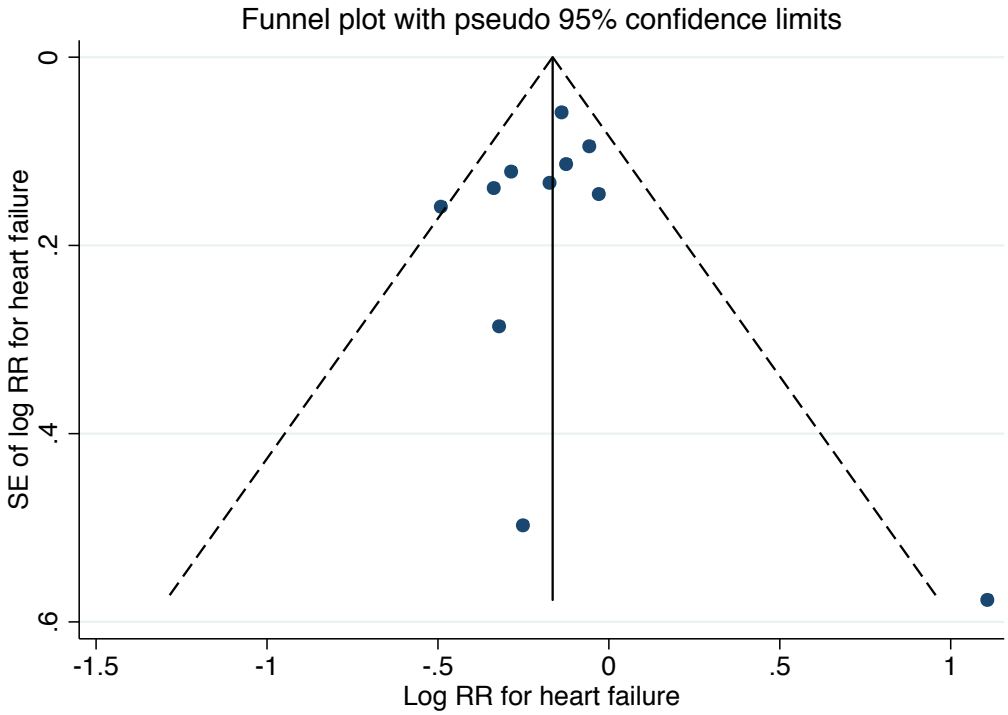
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.599

eFigure 22 – Funnel plot for stroke



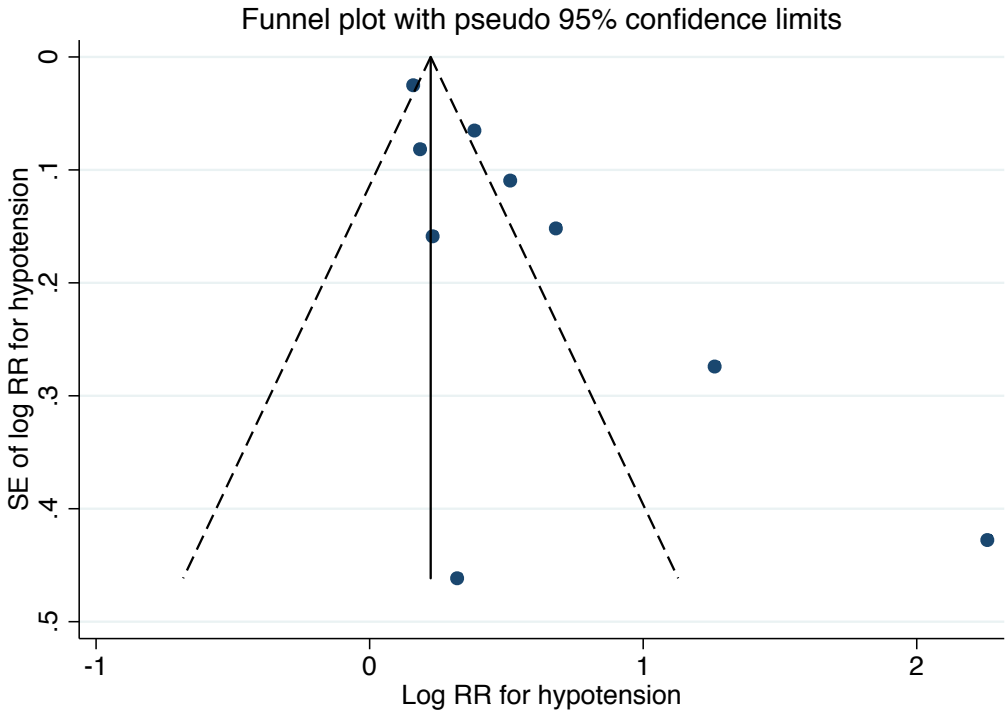
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.267

eFigure 23 – Funnel plot for heart failure



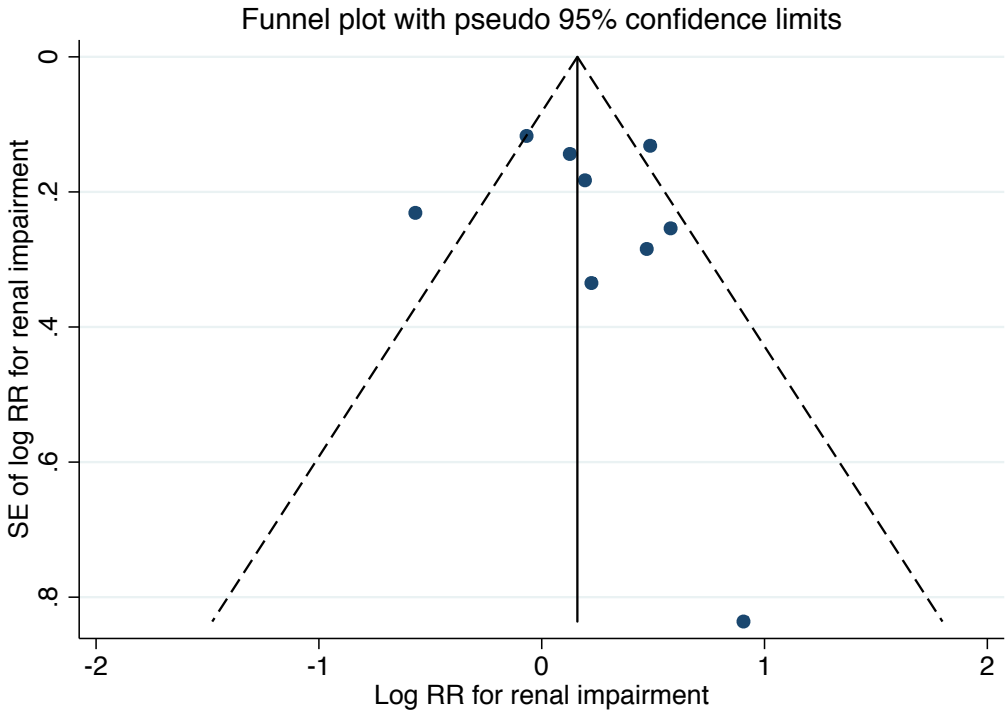
RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.854

eFigure 24 – Funnel plot for hypotension-related adverse events



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.060

eFigure 25 – Funnel plot for renal impairment



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.655

eTable 1 – Studies excluded due to high risk of bias or missing data

Study ID	Reason for exclusion
DIRECT Prevent 1[1] DIRECT Protect 1[1] DIRECT Protect 2 [1,2]	Cardiovascular events were evaluated as adverse events, and therefore not blinded. Also, cardiovascular events were not followed-up in people who discontinued treatment, meaning that > 700 patients were lost to follow-up regarding these events. Based on the above, we judge the DIRECT trials to be at high risk of both detection bias and attrition bias.
EUCLID [3]	No outcome data
HDFP [4]	Patients in the intervention group and patients in the control group were treated at different clinics. We therefore judge this trial to be at high risk of performance bias.
Hunan study [5]	Original publication could not be retrieved. Data from previous meta-analyses were of uncertain quality. For example number of strokes differed by tenfold in the analyses by Ettehad et al. and Law et al. Risk of bias assessment could not be made.
INTACT [6]	No blood pressure difference between groups.
MDRD [7]	No outcome data.
NICOLE [8]	No blood pressure data.
PATS [9]	30 % of patients were lost to follow-up. This was about five times the number of events, which means this trial is at high risk of attrition bias.
STONE [10]	Randomisation likely to have failed based on large difference in number of participants in each treatment arm. We judged this trial to be at high risk of selection bias.
Suzuki -08 [11]	All patients received hemodialysis and there was no difference in blood pressure between treatment groups. Although hemodialysis was not a pre-specified exclusion criteria, it alters physiology, affecting blood pressure and drug pharmacokinetics in such a way that the results in these patients are not applicable to the general population.
Syst-China [12]	Treatment allocation was not random. Therefore this trial is at high risk of selection bias and does not fulfil the inclusion criteria of this systematic review.
USPHS [13]	> 30 % of patients dropped out, not specified how many were lost to follow-up respectively followed for outcomes. Vital status not known for 26 patients, compared to 6 deaths. This suggests high risk of attrition bias. Furthermore, treatment groups differed by 2 mm Hg in systolic blood pressure at baseline, and 60 % vs 40 % on prior antihypertensive therapy.

Note: Several of the studies presented above were outside the eligible blood pressure range. They are presented here because exclusions based of risk of bias were done before selection on blood pressure data.

eTable 2 - Absolute risk of MACE in primary preventive trials

Study ID	Pts (n)	MACE (n)	Follow-up (y)	10-year MACE-rate (%) *
ACTIVE I	9016	1926	4.1	52
ALTITUDE	8561	1129	2.7	49
BCAPS	793	18	3.0	7.6
DREAM	5269	56	3.0	3.5
HOPE-3	12705	539	5.6	7.6
Lewis -93	409	-	3.0	-
NAVIGATOR	9306	752	6.5	12
PHARAO	1008	13	3.0	4.3
PREVEND-IT	864	42	3.8	13
ROADMAP	4447	-	3.2	-
Ravid -98	194	-	6.0	-
VA-NEPHRON	1448	270	2.2	85

Pts = participants. MACE = major cardiovascular events.

* 10-year MACE-rate was calculated as (MACE/Pts)x(10/duration).

eTable 3 - Risk of bias table

Study acronym	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
ACTION [14]	Low	Low	Low	Unclear	Low	Low	Low
ACTIVE I [15]	Low	Low	Low	Low	Low	Low	Low
ALTITUDE [16]	Low	Low	Low	Low	Unclear	Low	High
BCAPS [17]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
DREAM [18]	Low	Low	Low	Low	Unclear	Low	Low
EUROPA [19]	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
HOPE [20]	Low	Low	Low	Low	Low	Low	High
HOPE-3 [21]	Low	Low	Unclear	Low	Low	Low	Low
Lewis -93 [22]	Low	Low	Low	Low	Low	High	Low
NAVIGATOR [23]	Low	Low	Low	Low	Unclear	Low	Low
PART-2 [24]	Low	Low	Low	Unclear	Low	Low	Low
PEACE [25]	Low	Low	Low	Unclear	Low	Low	Low
PHARAO [26]	Low	Low	Unclear	Low	Low	Low	Low
PREVEND-IT [27]	Low	Low	Low	Low	Unclear	Low	Low
Ravid -98 [28]	Low	Low	Low	Low	Unclear	Low	Low
ROADMAP [29]	Low	Low	Low	Unclear	Low	Low	Low
SCAT [30]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
VA-NEPHRON [31]	Low	Low	Low	Unclear	Unclear	Low	Low

eTable 4 - Hypotension-related adverse events

Study ID	Pts (n)	Events (n)	RR for hypotension
NAVIGATOR	8 401	3 644	1.17
ACTION	7 305	558	1.20
HOPE	9 297	158	1.26
VA NEPHRON	1 409	19	1.38
ALTITUDE	8 339	876	1.47
HOPE-3	12 592	347	1.67
ACTIVE I	8 976	191	1.98
EUROPA	12 215	77	3.53
ROADMAP	4 341	64	9.56

Note: the apparent asymmetry in the funnel plots is not primarily due to smaller studies having extreme results; rather studies with few events show larger relative risks. This should be interpreted cautiously, but might represent different thresholds for reporting adverse events in different trials, with larger relative risks for more severe events.

eResults - Risk of bias assessment and description

Risk of bias was judged as low when we found a clear description that fulfilled the criteria for low risk of bias according to Cochrane Collaborations risk of bias assessment tool. Risk of bias was judged as unclear if we could not find an adequate description, or if the described methods did not fulfil the criteria for either low or high risk of bias. High risk of bias was assigned when we found a description of a study characteristic of methodological feature known to be associated with biased effect estimates.

All included studies were described as randomized double-blind placebo-controlled trials. Studies judged be at unclear risk of bias for the first three domains generally provided no further description of how randomization and/or blinding was achieved, yet we have no reason to believe it failed. Trials judged to be at unclear risk of bias in the forth domain generally described that outcomes were assessed by a separate committee, but did not explicitly describe this committee as blinded.

Several trials were judged to be at unclear risk of bias for incomplete outcome data. We used this label when attrition was small and asymmetric (ALTITUDE), or when loss to follow-up-rates were higher than event-rates (others). None of the included trials had large and asymmetric loss to follow-up.

Lewis -93 reported myocardial infarction, stroke, and heart failure for both groups combined, and is therefore judged to be at high risk of bias for these outcomes. This is not likely to affect overall results, however, because Lewis -93 was a small study with very few events compared to overall analyses.

We assessed early termination, changes in protocol and sponsor involvement as other potential sources of bias. In EUROPA, the definition of the primary outcome changed during follow-up. Although this might affect the interpretation of the study findings, outcomes used in our analyses where based on pre-defined criteria and not on whether they were primary or secondary in individual studies. Thus it should have little impact on our analyses.

ALTITUDE and HOPE were stopped pre-term due to interim findings. ALTITUDE was stopped due to an increased risk of stroke in the intervention group, whereas HOPE was stopped due to decreased risk of major cardiovascular events in the intervention group. To test the impact of these trials on overall results, we performed ad-hoc sensitivity analyses where they were excluded. Exclusion of ALTITUDE from the primary preventive stroke analysis moved the estimate slightly more towards benefit (relative risk 0.83, 95 % confidence interval 0.68-1.01, compared to 0.89, 0.73-1.09 when ALTITUDE was included). Exclusion of HOPE from the MACE analysis for CAD trials moved the estimate slightly towards neutrality (0.88, 0.78-0.99, compared to 0.85, 0.77-0.94 when HOPE was included).

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8 + Suppl.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8 + Suppl.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8 + Suppl.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Suppl.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 1 & 2 Suppl.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12 Fig. 1 & 2 Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13 + Suppl.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13 + Suppl.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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